1989 Hirayama publishes nested case-control results in *Present and Future of Indoor Air Quality*. Positive association of husband's smoking and lung cancer with dose-response pattern reported after adjustment for dietary variables.

A.13.2. Some Major Critical Works

A basic point raised by MacDonald (1981) and others soon after publication of Hirayama's initial results concerns the selection of the study's sample population. It appears that the 29 health centers included in the study were selected on grounds of convenience rather than to provide a randomly sampled, representative cross-section of the Japanese population. The resultant sample may thus be unrepresentative of the Japanese population as a whole.

A convenience sample may still produce a fairly good cross-section of the population, and Hirayama replied in 1981 that "the satisfactory representativeness [of the study population] . . . with regard to demographic and social indices was confirmed after the survey." He did not, however, provide supporting data. MacDonald (1981) contends that the six prefectures from which the sample was drawn are relatively industry-heavy (which does not necessarily contradict Hirayama's contention); data presented by Hirayama (1983) showed that 40,390 of the cohort's wives were married to agricultural workers, 19,264 to industry workers, and 31,886 to "others," which would indicate some overrepresentation of agricultural areas. Women aged 70 or more are clearly underrepresented, composing less than 1% of the study's 40-and-older nonsmoking female population. Thus, the cohort may be unrepresentative to some degree, but *how* unrepresentative is unclear.

The key problem arising from an unrepresentative sample is that it may limit generalizability of results derived from that sample to the population as a whole. In lieu of good reasons to think that the association between exposure and disease would be different in the study population and the general population, however, the possibility of an unrepresentative sample assumes less importance. And, as will be seen in the subsequent discussion of possible confounders, similar patterns of association were observed in a number of demographic sub-groups.

Misclassification may occur in any epidemiologic study. Most of the critical commentary has focused on potential misclassification of exposure status. Because the study relies on interview data to establish smoking status, misreporting by interviewees may affect accurate classification of both wives *and* their husbands' smoking habits. It has been argued that women are especially likely to misrepresent their smoking habits because smoking is considered less socially acceptable for women than for men, particularly in Asian societies. Such misclassification

would tend to reduce the degree of association between passive smoke exposure and its effect(s) if women in the "exposed" and "unexposed" groups were equally likely to misreport their own smoking. One of the most prominent criticisms leveled at the Hirayama study postulates a differential misclassification of smoking status in women. Peter Lee (Lehnert, 1984) raised the argument that if women married to smokers are more likely to be (or to have been) smokers than are women married to nonsmokers, and a given percentage of smoking women claim to be nonsmokers, then purportedly nonsmoking wives of spousal smokers will include a higher proportion of active smokers than wives of spousal nonsmokers. This will cause bias in the direction of a positive association. Arguments over the probable size of this bias have occurred with estimated elevations in risk ranging from a few percent to around 50%, depending on assumptions regarding the extent of misreporting, the risk inherent in active smoking, and the degree of marital concordance between smokers (Lehnert, 1984; Wald et al., 1986; Lee, 1987a and b).

Uberla and Ahlborn (1987) raised a number of points regarding the Hirayama study, including those previously mentioned. Citing the "severe selection bias by age," the authors report that the increase in risk with spousal smoking disappears when this bias is corrected for. The study population in fact contained a very small proportion of women aged 70 or more (only about 1%)—so small that the rates generated by nonsmoking married women aged 70 or more are too unstable to provide meaningful results. But by taking the negative results observed in this tiny, unstable stratum of the cohort and weighting them to "correct" for the underrepresentation of this age group, the overall association is made to disappear. Such a "correction" is meaningless. In addition, Hirayama (1990) has noted that the authors inappropriately adjusted to the total female population rather than to the population of currently married females, and characterized the adjustment as "neither of scientific significance nor of creative value."

The authors also essentially take Lee's approach to the differential misclassification problem and claim that a modest differential misclassification "leads to risk ratios of around unity." As seen previously, this argument is plausible but purely speculative—and, of course, potential biases toward the null are ignored in this and other "corrections." The authors conclude that "the null hypothesis . . . is consistent with the Hirayama data in the same way as the alternative." But unless one applies the aforesaid "corrections," the Hirayama data is, in fact, *more* consistent with the hypothesis of association than with the null hypothesis.

Layard and Viren (1989) estimated "projected" mortality rates for a cohort with the age and time distribution found in the Hirayama cohort by applying "standard demographic life table procedures" to year and age-specific life table data from United Nations and Japanese sources.

They concluded that female all-cause and lung cancer reported rates were only 76% and 85%, respectively, of projected values. In a separate analysis, the authors also "calculated the numbers of person-years that would have been observed in the cohort if there had been 100% follow-up" from the reported numbers of deaths. The assumptions used in this calculation are unstated. The authors then estimated, based on the difference between their person-years for 100% follow-up and the reported person-years, and an assumption that 8 years of observation were lost on average for each person lost to follow-up over the 16-year course of the study, that approximately 10% of the cohort was lost to follow-up. Dismissing other possible causes of their estimated mortality deficits, Layard and Viren conclude that "it is possible that biases exist in the data which might invalidate an observed relationship between exposure to ETS and mortality."

Of course, acceptance of Layard and Viren's conclusions must start with acceptance of the validity of their assumptions and calculations, not all of which are stated explicitly. Beyond that, their rejection of alternative explanations for the difference between projected and reported deaths is not convincing. For example, random sampling variation and regional variations in death rates are both dismissed because neither could produce an effect as large as that observed, although the authors' figures indicate that in combination they could well account for a sizeable portion of the difference. Likewise the effect of admitting only (initially) "healthy" people to the cohort is dismissed based on the observation of "still very substantial cohort deficits in the last years of the study" without specification of how substantial such deficits were and ignoring the fact that a pattern in which all-cause mortality is most affected and cancer mortality least, as their calculations showed, is the expected pattern for an effect of selection of healthy individuals. Finally, to produce a spurious association, a bias must operate differently on the exposed (smoking spouse) and unexposed (nonsmoking spouse) groups, and no evidence is provided that supports such a pattern. Lacking such a pattern, the most likely effect of loss to follow-up is a reduction in the observed associations due to missing mortality events. The effect of selecting an abnormally healthy cohort would in a strict sense limit generalizability of conclusions but would not in itself produce an exposure-effect association when none actually existed.

A.13.3. Critique and Assessment

Hirayama's cohort is drawn from a study population assembled to explore the associations between a number of potential health-influencing factors determined via interview and subsequent mortality. Thus, the study was not designed to investigate passive smoking and lung cancer specifically. Most of the weaknesses attributable to Hirayama's study derive from this fact.

The only indicator of ETS available to Hirayama was self-reported smoking status at time of baseline interview. Thus, misclassification of spousal smoking status is possible and change in status over time, modifiers of exposure to spousal smoking, and other sources of ETS exposure cannot be determined.

As previously seen, an overrepresentation of current and former active smokers claiming to be nonsmokers among wives of tobacco smokers probably biases the association between spousal smoking and lung cancer in reported nonsmokers upward. Even the leading proponent of this argument, however, states that unless this bias is much stronger than it appears to be in U.S. and Western populations, it could not account for the major part of the observed results (Lee, 1990). Lack of information regarding amount of smoking actually done in the home and in the presence of the spouse, room size and ventilation, and other exposure modifying factors must lead to imprecision in the estimates of exposure via spousal smoking. This imprecision would make an actual ETS-lung cancer association more difficult to detect. The fact that spousal smoking exposure, even if precisely measured, is an imperfect surrogate for total ETS exposure because workplace and ambient environmental sources are not assessed introduces a similar effect. Both of these problems would thus introduce a bias toward the null, suggesting that the study's results are an underestimate of the real association.

Mortality information was derived from death certificate linkage. It has been contended that lung cancer is routinely overdiagnosed as a cause of death on death certificates, thus undermining the study's credibility. But the resultant misclassification of cause of death would presumably be nondifferential and thus bias results toward the null. To cause overestimation of the association, a greater proportion of women in the spousal smoking groups than in the nonsmoking group would have to be falsely diagnosed as having lung cancer. Because the study cohort was made up of *nonsmoking* women, there would be little reason for such a pattern. (Unless, of course, all such cases came from women who falsely reported their initial smoking status or took up smoking in the course of the study *and* the misclassification/smoking habit concordance hypothesized by Lee were actually strongly at work.)

No information is given regarding whether the same interviewers interviewed both husbands and their wives. Thus, interviewers may not have been blind to spousal smoking characteristics of interviewees. This is likely to have been of little importance, however, because the outcome—lung cancer mortality—was measured prospectively, and thus did not occur for some time *after* exposure had been assessed. If information bias was to some extent operant in the interview, the most likely scenario would find women whose husbands smoked being probed more strongly for admission of their own smoking than were women whose husbands did not smoke.

This would tend to *reduce* underreporting of active smoking in the "exposed" group relative to the "unexposed" group. The result would be to *lower* the observed association between husbands' smoking and lung cancer mortality.

Hirayama's cohort includes only married, reportedly nonsmoking women who were at least 40 years of age and "healthy" at the start of the study. In addition, almost all of these women were under 70 years of age, and agricultural families composed a relatively large part of the cohort. Thus, the cohort does not present a representative cross-section of the Japanese population as a whole. Nevertheless, there is little obvious reason why a relationship between spousal smoking and lung cancer mortality found in this cohort should be dismissed on the grounds that it is not generalizable to the greater Japanese (or other) population. In fact, one could argue that by studying a more homogeneous population in the cohort, the possibilities for bias due to differences between exposed and unexposed groups are reduced.

The possibility that confounding by other risk factors brought about an observed association must be considered in any study. For lung cancer, of course, smoking, gender, and age are major risk determinants. Restriction of comparison groups to same-gender nonsmokers avoids potential confounding by gender or smoking (but see misclassification discussion regarding smoking status). Age is only partially restricted in the study design, so its consideration in the analysis is essential. Hirayama chose to control for husband's age in analyzing the cohort study's results. All observed associations persisted after such adjustment. Spousal ages *should* be closely correlated, but direct adjustment using the subject's own age rather than the age of their spouse would clearly be preferable. One such analysis *was* supplied (Hirayama, 1983b), and in it a significant association between spousal smoking and lung cancer mortality persisted. Furthermore, in analyzing the nested case-control studies, adjustment for wife's age was used throughout, which produced findings that confirmed the results of the cohort study.

The potential role of confounding by other factors in the observed results has received considerable emphasis. A correlation between smoking and lower socioeconomic status with concomitant lifestyle and environmental differences could be expected. Among these differences, particular attention has been paid to the possible effect of dietary factors, particularly low beta carotene intake, and occupational exposures, both of which, some hold, should correlate with spousal smoking and thus could bring about the observed association even if spousal smoking and ETS exposure has no effect. Yet, neither stratification on daily green-yellow vegetable consumption—the best available surrogate for beta carotene intake in the data—nor on agricultural versus nonagricultural occupation of husband eliminated the association between spousal smoking and lung cancer mortality in the cohort study. Similarly, adjustment for husband's occupation and

any of five dietary habit characteristics, along with wife's age, yielded similar results in the case-control approach. Thus, neither of the major proposed confounders satisfactorily accounts for the observed results.

Because the data set does not contain the necessary information to examine confounding due to differences in cooking practices (such as stir-frying), this cannot be ruled out, although such practices might be expected to covary with some of the dietary factors considered in the analyses. Similarly, use of coal for cooking or heating cannot be directly assessed, though a degree of covariance with dietary habits or occupation is likely.

Husband's drinking habits were only marginally associated with lung cancer risk; mortality rates stratified by both drinking and smoking would have been more useful (and stratification by wives own drinking habits would have been more useful still).

When lung cancer mortality among wives is stratified by wife's age (in 10-year increments) and husband's smoking category, a clear dose-response pattern is seen only in the 40 to 49 and 50 to 59 age strata, whereas a decrease in mortality with spousal smoking is seen in the 70 and older stratum. Given that the latter stratum includes less than 1% of the cohort and very few deaths, its rates are too unstable to have much confidence in. The dose-response pattern does become weaker with ascending age strata, however, which has led to conclusions of inconsistency with an ETS-lung cancer connection and presence of confounding. Hirayama has proposed that age-related increases in spousal mortality, smoking cessation, and decreased time spent in husband's proximity during the follow-up period may account for the observed pattern (Hirayama, 1990). The proximity effect seems questionable, because retirement of older husbands would eliminate time spent away from the house at work, but the other arguments are plausible. Alternatively, older women recently married to smokers may be more likely to die from competing causes of death that increase with age before passive-smoke cancer develops. Remarriage, possibly to a spouse whose smoking habits differ from those of the former spouse, would also increase with age and could lead to misclassification of (former) exposure with a bias toward the null. (It is unfortunate that history of former spouses' smoking habits and recency of marriage were apparently not obtained in the baseline interview or the aforementioned problems could be readily addressed.) Temporal trends in some risk modifiers, such as dietary factors, could also play a role.

Confounding cannot entirely be ruled out in certain instances. But the underlying question that must be raised in this regard is the following: *If* the spousal smoking group contains a disproportionate number of individuals with risk-elevating factors such as poor diet, lack of exercise, low socioeconomic status, and occupational hazard exposure, and these factors are

sufficient to produce an increase in lung cancer mortality relative to the spousal nonsmoking group, despite an absence of any real smoking effect, *why* does this multitude of risk factors result in elevations of established smoking-related diseases only and no substantial elevation of risk of other causes of mortality (except brain cancer, which encompasses relatively few deaths)?

In considering the study's results in broader terms, Hirayama's findings are consistent with the hypothesis that exposure of nonsmoking women to passive smoke via spousal smoking increases risk of lung cancer. The observed association is statistically significant. And the persistence of the association after stratification on numerous variables, the observation of a parallel association in nonsmoking husbands of smoking wives, the appearance of associations with other smoking-related diseases, the existence of a dose-response pattern in most analyses of strata containing adequate numbers, and the production of similar conclusions by either cohort or case-control approaches argues against attribution of results purely to chance or confounding.

Possible inclusion of active smokers among "nonsmoking" spouses of smokers through misclassification bias or differential change in smoking status during follow-up remains the study's greatest weakness. This problem could have been addressed by follow-up interviews or questionnaires coupled with verification of smoking status by alternative means in a subsample of the cohort, and still could be. In addition, losses to follow-up and failure to use more sophisticated survival analysis techniques are weaknesses that probably reduced the study's power.

Overall, the Hirayama study provides supportive, although not definitive, evidence that ETS exposure increases lung cancer risk.

A.14. HOLE (Coh)

This prospective cohort study was undertaken in the towns of Paisley and Renfrew, Scotland. The primary objective was to explore the relationship between passive smoking and cardiorespiratory symptoms and mortality, including lung cancer. The towns were selected because they are situated in an area with a high incidence of lung cancer. All persons residing in these towns between 45 and 64 years of age, inclusive, were visited between 1972 and 1976. Each was asked to complete a self-administered questionnaire and to visit a cardiorespiratory screening center where further interviews were conducted; 80% (15,399 persons) responded.

Participating households in which at least two "apparently healthy" subjects lived were included in the study, yielding a study population of 3,960 males and 4,037 females. Data on smoking habits were obtained from the questionnaire and verified by interview at the screening visit. Mortality among subjects was traced using the Scottish National Health Service Central Register and General Register offices (for death certificate linkage), as well as the national cancer

registry system. Results for follow-up through 1982 were published in 1984 (Gillis et al., 1984). The primary results reported here are for follow-up through 1985, published in 1989 (Hole et al.). In addition, the results of unpublished data extending follow-up through December of 1988 are reported (personal communication from Hole to A.J. Wells).

Smoking habits were divided into three categories: persons who have never smoked, former smokers, and current smokers. In addition, the number of cigarettes smoked per day was obtained for current smokers. Both pipe and cigar smokers were excluded from the group who had never smoked. Never-smokers with former or current smokers as cohabitants in their household were classified as passive smokers; otherwise never-smokers were classified as "controls." This classification yielded 1,538 passive smokers and 917 controls for both sexes combined. The corresponding numbers for females alone are 1,295 and 489.

The number of lung cancer deaths among females occurring in the cohort during the follow-up period is only six, too small to be of statistical consequence. The unpublished data extending follow-up through 1988 includes one additional female lung cancer death that occurred subsequent to 1985. The crude relative risk is 2.27 (95% C.I. = 0.40-12.7), which is in the direction of a positive association between ETS exposure and lung cancer. The extremely wide confidence interval is the result of the small number of cancer deaths being compared and indicates that the data could easily arise when the true value of the relative risk is almost any value. After adjustment for age and social class, the relative risk is 1.99 (95% C.I. = 0.24-16.72). Lung cancer incidence was somewhat higher than mortality (10 cases vs. 7 deaths), yielding an adjusted relative risk of 1.39 (95% C.I. = 0.29-6.61). The relative risks for adjusted mortality (5.30) and incidence (3.54) were higher in males than in females but were based on even fewer cases (four deaths, six incident cases).

Although the observed association could easily occur by chance, it is a useful contribution to the pool of evidence on lung cancer and passive smoking. Consequently, it is worth noting that the observed associations are not likely to be attributable to confounding by other factors, because they persisted after control not only for age and gender, but for social class, diastolic blood pressure, serum cholesterol, and body mass index. Thus, differences in lifestyle or environmental factors such as diet, housing, and employment between passive-smoking households and nonsmoking households is an unlikely source of the results. Specific adjustment for potential occupational exposures or radon were not carried out, but these variables would presumably covary with social class to a great extent.

As for other sources of bias, interviewer bias can be discounted because subjects were "apparently healthy" at interview and supplied smoking information before cardiovascular

screening, and the investigators did not begin determining the passive smoking status of subjects until 1983 (for the first published study on this cohort). The extent of loss to follow-up is not specified, so one cannot tell whether this was a potential source of problems. However, linkage was carried out through two registries for general mortality and an additional registry specifically designed for cancers. Diagnoses of cancer mortality from death certificates were checked against cancer registry records for verification, thus reducing potential inaccuracies attendant on use of death certificates.

Some data regarding misclassification were collected in an additional questionnaire administered to a portion of the cohort at some unspecified point in the study. Among controls, 5% said that their household contained a smoker—presumably someone who had not met the inclusion criteria (e.g., age 45-64) for the study. Thus, a small portion of the control group was actually currently exposed, which would produce a slight bias toward the null. Differential misclassification of smokers as never-smokers resulting from concordance of smoking habits among cohabitants cannot be assessed or ruled out, despite the authors' suggestion that persons cohabitating with smokers may be more likely to falsely claim to be smokers themselves, providing a bias toward the null.

In summary, this study appears well-designed and executed, but the number of ETS exposed subjects is small. Although its influence may be relatively small, there are no apparent methodological problems that would limit its usefulness otherwise.

A.15. HUMB

A.15.1. Author's Abstract

"As part of a population-based case-control study of lung cancer in New Mexico, we have collected data on spouses' tobacco smoking habits and on-the-job exposure to asbestos. The present analyses include 609 cases and 781 controls with known passive and personal smoking status, of whom 28 were lifelong nonsmokers with lung cancer. While no effect of spouse cigarette smoking was found among current or former smokers, never smokers married to smokers had about a two-fold increased risk of lung cancer. Lung cancer risk in never smokers also increased with duration of exposure to a smoking spouse, but not with increasing number of cigarettes smoked per day by the spouse. Our findings are consistent with previous reports of elevated risk for lung cancer among never smokers living with a spouse who smokes cigarettes."

A.15.2. Study Description

This population-based case-control study was conducted through the New Mexico Tumor Registry during 1980-84. The original purpose was to explain differing lung cancer occurrence in Hispanic and non-Hispanic whites in New Mexico. The study questionnaire included questions on spousal smoking and on indirect exposure to asbestos through a spouse's job. The current report describes the risks associated with those exposures in smokers and nonsmokers. The data on ETS exposure in nonsmokers is extracted from the larger study containing smokers.

For the whole study, a total of 724 eligible primary lung cancer patients were identified, of which 641 were interviewed (89%). About half (48%) of the case interviews were conducted with the subject. Information on the remaining subjects was obtained from surrogates, generally the surviving spouse or a child. Cases were collected in two series, the first consisting of patients with cancer incident in 1980-82. That group includes all cases less than 50 years of age and all Hispanics, but not those exclusively. The number of cases was supplemented by a second series of patients with cancer incident to a 1-year period beginning November 1983. Most of the controls were selected by random telephone sampling, but some older subjects were randomly selected from Medicare participants. The control group was frequency-matched to the cases for sex, ethnicity, and 10-year age category, at a ratio of approximately 1.2 controls per case. Interviews were held for 784 of the 944 eligible controls, with 98% of the responses from subjects.

The term "never-smoker" means not a cigarette smoker, where the latter is defined to be someone who has smoked at least 6 months. The smoker classification is divided further into current smokers and ex-smokers. The current smoker status includes smokers who have stopped within 18 months prior to the interview; the ex-smoker status applies if smoking ceased more than 18 months prior to interview. Assuming that the minimum 6-month duration of smoking is intended to apply to current and ex-smokers, never-smokers could have smoked previously for up to 6 months.

An ETS-exposed subject is one ever-married to a spouse who smoked cigarettes, regardless of the spouse's use of pipes or cigars. No information was obtained on exposure to ETS from other sources, such as from other household smokers, in the workplace, or from parental smoking during childhood. Measures of ETS exposure from spousal smoking include duration of exposure (in years) and the average number of cigarettes smoked per day by the spouse. The ETS subjects (never-smokers) include 20 (4) female (male) cases and 162 (130) controls (the article reports eight male cases, the number used in much of the analyses, but four of those eight were found to be smokers—personal communication from Humble). The age distribution for the female cases (controls) is as follows: age less than 65, 5 (74); age 65 or more, 15 (88).

The odds ratio for the crude data on female never-smokers is 1.8 (90% C.I. = 0.6-5.4) for spousal smoking of cigarettes only and 2.3 (90% C.I. = 0.9-6.6) when spousal smoking also includes use of pipes and cigars. Based on mean cigarettes per day smoked by the spouse, the odds ratio of 1.2 at more than 20 cigarettes per day is somewhat lower than the odds ratio of 1.8 at the lower rate, less than 20 cigarettes per day. For duration of exposure, the odds ratio increases from 1.6 at less than 27 years to 2.1 at 27 or more years. It is reported that adjustment for age and ethnicity did not alter these results from the crude analysis. A trend test is included for duration of spousal smoking, but the sample sizes are too small to be meaningful. Application of logistic regression to adjust for variables gives values very close to the odds ratios for the crude analyses shown above for spousal smoking, for use of cigarettes only and also for combined use of cigarettes, cigars, and pipes.

The distribution of cases by cell type is given, but only with males and females combined. The ratios of ETS-exposed cases to the total, by cell type, are as follows: squamous cell (2/4), small cell (1/1), adenocarcinoma (either 6/12, 7/12, or 8/12), and others (either 3/3, 2/3, or 1/3, depending on correct ratio for adenocarcinoma).

The authors conclude that the results indicate increased risk from ETS exposure in never-smokers but not in active smokers.

A.15.3. Comments

This study evaluates smokers as well as nonsmokers for increased risk of lung cancer from spousal smoking. Not surprisingly, the number of smokers among the cases far outweighs the number of nonsmokers. No evidence of added risk to smokers from passive smoking is found. Such an evaluation, however, puts a great deal of faith in the exposure data and the power of statistical methods to detect what may be only a marginal increase in risk from ETS on top of active smoking.

Of more central concern to this review is the assessment of lung cancer from ETS exposure in never-smokers. The ETS data are taken from a larger study, so the matching no longer applies, although the adjustment for those variables (ethnicity and age category) in the analysis is worthwhile. The article suggests that the high rate of proxy response for cases in the original study (52%) may be due, at least in part, to inclusion of decedent cases. That topic is not explicitly addressed, however, and controls were not matched to cases on vital status. Never-smokers apparently may have a history of smoking, provided it is under 6 months' duration. Whether any never-smokers actually have a short smoking history is not discussed, but the never-smoker classification is less strict than in most studies.

The data are evaluated a number of different ways, consistently yielding an increased odds ratio. The number of cases, however, is much too small (15 exposed, 5 unexposed) for the observed odds ratio to be close to statistical significance. Although similar values of the odds ratios might be observed in a larger study, that cannot be assumed. At most, the study outcome is suggestive of a possible association between ETS exposure and lung cancer occurrence, in need of additional support to be conclusive. Overall, this study is conducted well in many respects, but its contribution to the pool of evidence for assessment of lung cancer and ETS exposure is tempered by several weaknesses, as described above.

A.16. INOU

A.16.1. Author's Abstract

A case-control study on smoking and lung cancer in women was conducted in Kamakura and Miura, both in Kanagawa prefecture, Japan. The two cities are distinctly different in social environment; the former is a residential community, and the latter is a fishing village. After stratification on city and age groups, the odds ratio of lung cancer in nonsmoking wives was shown to be 1.58 when husbands smoked fewer than 19 cigarettes a day and 3.09 when husbands smoked 20 or more cigarettes a day. For comparison, the odds ratio for active smoking is 5.50. Although the study size is quite small, it provides additional evidence favoring the passive smoking and lung cancer hypothesis. (Paraphrased from author's discussion; no abstract was provided.)

A.16.2. Study Description

This study was conducted to assess the roles of active and passive smoking in the etiology of lung cancer in women. It is unclear how subjects or diagnoses were obtained, but cases are women who died of lung cancer in Kamakura or Miura in the time periods 1980-83 and 1973-81, respectively. Controls, consisting of women who died of cerebrovascular disease during the same time frames, are individually matched to cases on year of birth, year of death (± 2.5 years), and district of residence. It is not clear whether incident cases were used.

Face-to-face interviews were conducted by public health nurses and midwives. ETS subjects consist of the 28 nonsmoking cases and 62 nonsmoking controls remaining after elimination of 9 cases and 12 controls who were smokers. Husband's smoking status was not available for unspecified reasons in a total of 8 cases and 20 controls, but these figures include smokers as well as nonsmokers. The exact number of nonsmokers for which spousal smoking status was available is not specified but can be back-calculated from what is given (see below).

No information is given on the number of proxy respondents, the age distribution of the subjects, or attempts to confirm diagnoses of primary lung cancer.

The term "nonsmoker" is not defined, so it is not clear whether it refers to persons who never smoked or who do not smoke at present. Nonsmoking women whose husbands smoke at least five cigarettes per day are classified as exposed to passive smoking. Considerations of former smoking or marital status, ETS exposure at the workplace or in childhood, and duration of exposure are not addressed. No attempts to verify the reliability or validity of the data are mentioned.

The number of subjects is not delineated by case versus control and exposed versus unexposed figures. They can be determined from the odds ratio and confidence interval, however, as 18 out of 22 (exposed over total) cases and 30 out of 47 controls. For nonsmoking women with smoking husbands, the crude odds ratio calculated by the reviewers is 2.55 (95% C.I. = 0.74-8.78). (*Note:* OR = 2.25 is erroneously reported in the article. The OR value of 2.55 has been confirmed by Hirayama.) When husbands' smoking is divided into two strata ($<$ 19 cig./day and 20+ cig./day), the odds ratios increase with exposure from 1.16 to 3.35, giving a statistically significant trend ($p < 0.05$). Age-adjusted odds ratios of 1.39 and 3.16 are reported for the two strata; adjustment for both age and district yields corresponding odds ratios of 1.58 and 3.09. (*Note:* The first OR value, 1.58, is incorrectly reported as 2.58. The value 1.58 has been confirmed by Hirayama.) The authors conclude that, although the study size is quite small, the results provide more evidence favoring the hypothesis that passive smoking causes lung cancer.

A.16.3. Comments

The number of subjects remaining after active smoking and missing data exclusions is small, guaranteeing poor power and lack of statistical significance in the absence of large odds ratios. The details on study design are limited. The source of cases and controls is not mentioned, for example, and it is unclear whether incident or prevalent cases were used.

Information regarding quality control and related concerns is equally sparse. Interviewers used standardized questionnaires, which would help to promote consistency, but no mention is made of blinding them to subject background or study question, the absence of which could introduce interviewer bias (probably in a positive direction). Because cases and controls are stated to have died during the study period, it is probable that proxy respondents were required, but the extent is unknown. In addition, neither duration of ETS exposure from spousal smoking nor exposure from other sources, such as other cohabitants, was considered. The resultant inaccuracy of exposure assessment probably biases the results toward the null. Lack of information on

former smoking status or verification of diagnosis may introduce biases of indeterminate direction. Except insofar as the district acts as a surrogate for factors related to socioeconomic status, no potential confounders other than age or district of residence were considered. The meaning of "nonsmoker" is not given. Was that status left to self-classification? Is some degree of past smoking acceptable? Is smoking history a factor at all (i.e., does nonsmoking refer simply to the current status)? Accurate and meaningful segregation of never-smoking subjects is needed for analysis, but there is no indication that that was accomplished.

Although a substantial odds ratio was observed for husband's smoking, these results are based on a small sample with too few details provided to assess adequately either the evidence or the study's design and execution. The numerous sources of potential bias are enhanced by the omissions or sketchy descriptions of the study. The statistical uncertainty of the odds ratios given is reflected in the extremely wide confidence intervals shown. The test for trend does not add any additional information. It is basically a restatement of the significant comparison between the heavily exposed group (husband smokes > 20 cig./day) and the unexposed group. Unfortunately, the brevity of the description of this study in the source available severely limits its utility.

A.17. JANE

A.17.1. Author's Abstract

"The relation between passive smoking and lung cancer is of great public health importance. Some previous studies have suggested that exposure to environmental tobacco smoke in the household can cause lung cancer, but others have found no effect. Smoking by the spouse has been the most commonly used measure of this exposure.

In order to determine whether lung cancer is associated with exposure to tobacco smoke within the household, we conducted a population-based case-control study of 191 patients with histologically confirmed primary lung cancer who had never smoked and an equal number of persons without lung cancer who had never smoked. Lifetime residential histories including information on exposure to environmental tobacco smoke were compiled and analyzed. Exposure was measured in terms of "smoker-years," determined by multiplying the number of years in each residence by the number of smokers in the household."

A.17.2. Study Description

This study was undertaken in New York State to clarify the role of exposure to tobacco smoke in the household as a possible cause of lung cancer among nonsmokers. Interviews were conducted with former as well as never-smokers initially (Varela, 1987), but because matching

was carried out on smoking status, only never-smoking case-control pairs were included in the analyses for this article. The study includes both males and females, which are combined in all of the analyses. There are 146 (45) female (male) pairs.

Cases are never-smokers aged 20 to 80 years newly diagnosed with lung cancer at 125 referral centers in New York from July 1, 1982, to December 31, 1984. Controls are cumulatively sampled never-smokers identified from files of the New York Department of Motor Vehicles. Controls are individually matched to cases on age (± 5 years), gender, and residence. In addition, the same interview type (proxy or direct) was used for controls as for their corresponding cases. Exposure data were collected face-to-face via standardized questionnaire by interviewers blind to the subject's status.

From the 439 case-control pairs interviewed, 242 pairs containing former smokers and 6 pairs with a mismatch on the source of response were excluded. Of the remaining 191 pairs used in the ETS study, interviews were conducted directly with the subjects in 129 (68%) and with proxies in 62 (32%) (if a proxy was interviewed for a case, then a proxy was used for the matching control as well). No demographic comparisons were provided for the ETS cases and controls. For the whole study including smokers, the mean age of cases and controls is nearly identical (67.0 and 68.1, respectively; Varela, 1987). Histological verification of diagnosis was obtained for all but five cases (for whom only clinical information was available) out of the initial population of 439.

Persons smoking no more than 100 cigarettes over the course of their lifetime qualified as never-smokers for this study. Cigar or pipe smoking was apparently not considered. Exposure to ETS was deemed to occur when a smoker lived in the subject's household at any time from infancy to adulthood. Both total household smoke exposure and spousal smoke exposure were determined. Preadult (before 21 years of age) and adult exposure were examined separately. Exposures were computed in units of "smoker-years," the total number of years lived with each smoker summed over smokers. In addition, pack-years were calculated for spousal smoking. Workplace exposure also was estimated by smoker-years, whereas exposure in social settings was estimated subjectively on a scale from 1 to 12 for each decade of life and summed. Exposure data were not checked, and marital status was not considered in the analyses. No information on tumor type or location was provided for the never-smoking population.

Preadult exposure to 24 or more smoker-years occurred in 52 (29) cases (controls) whereas 82 (94) were exposed to 1 to 24 smoker-years and 57 (68) were unexposed. Odds ratios were calculated using matched-pairs regression analysis. Preadult passive smoking yielded increasing odds ratio of 1.09 (95% C.I. = 0.68-1.73) for 1 to 24 smoker-years and 2.07 (1.16-3.68) for 25 or more smoker-years. The odds ratios for adult exposure are low but also increase—from 0.64 (0.34-

1.21) at 1 to 24 smoker-years to 1.11 (0.56-2.20) at 75 or more smoker years. The odds ratios for lifetime exposure increase from 0.78 (0.36-1.67) at 1 to 24 smoker-years to 1.80 (0.83-3.90) at 25 to 99 smoker-years and then dip to 1.13 (0.56-2.28) at 100 or more smoker-years. Spousal smoking was not significantly associated with lung cancer. In fact, when results were stratified by type of interview, proxy interviews yielded strong and, in some instances, statistically significant *negative* associations for spousal smoking, with odds ratios between 0.20 and 0.68 for ETS expressed in terms of present or absent, smoker-years, and pack-years of exposure. The odds ratios for direct interviews, in contrast, range from 0.71 to 1.10 and are uniformly higher than the odds ratios for corresponding proxy responses. Workplace exposure to 150 or more person-years yielded an odds ratio of 0.91 (0.80-1.04), whereas a social setting exposure score of 20 led to a statistically significant *decreased* odds ratio of 0.59 (0.43-0.81).

The authors conclude that they found a significant adverse effect of relatively high levels of exposure to ETS during early life (before age 21). For those who were exposed to 25 or more smoker-years in their first two decades of life, the risk of lung cancer doubled. By contrast, they found no adverse effect of exposure to ETS during adulthood, including exposure to a spouse who smoked. This lends further support to the observation that passive smoking may increase the risk of subsequent lung cancer, and it suggests that it may be particularly important to protect children and adolescents from this environmental hazard.

A.17.3. Comments

The number of never-smoking cases is relatively large, resulting in above-average statistical power for evaluation of ETS effects. Controls were matched to cases on smoking status, as well as the key demographic factors of age, gender, and neighborhood. Comparability of cases and controls was likely good, as evidenced by the similar mean ages for the total population, although no other comparative information is available. Interviews were ostensibly conducted blindly, thus precluding interviewer bias, but in view of the use of population-based, basically healthy controls, it is questionable that diagnostic blinding was effective. The study's matching on smoking status with subsequent retention of matching and use of matched-pairs analysis for ETS exposure effectively eliminates potential confounding by age, gender, or residence, and makes confounding by related factors (such as socioeconomic status) less likely. A rare feature is the use of matching on interview type (i.e., proxy or subject direct), thus eliminating potential confounding by this source. Comparison of spousal smoking results for direct and proxy interviews, however, indicates consistently lower estimated risks from proxies. This suggests that use of proxy respondents did not merely lead to increased random misclassification but might

have biased the outcome toward a negative association. The authors posit that proxies of lung cancer patients may be more likely to underreport exposure than those of control subjects. Curiously, however, although the authors report that odds ratios "frequently differed according to type of interview," they do not specify how the odds ratios differed for exposure other than spousal smoking. Also, the composition of the proxy groups—relative proportions of spouses, other relatives, and friends or associates—is never discussed, leaving unexplored the possibility that misreporting by spouses of cases may lie at the heart of the observed discrepancy. It is also interesting that the outcome of self- versus proxy responses in this study is in the opposite direction of the findings in GARF. Diagnostic misclassification is unlikely, given the histological verification of nearly all cases.

The restriction of subjects to persons smoking no more than 100 cigarettes in their lifetime theoretically eliminates active smoking as a source of bias, although no verification of smoking status was undertaken. Consideration of potential sources of ETS exposure is commendably thorough, and the calculation of total years of living with smokers, regardless of relation to the smoker, as an index of household smoke exposure minimizes the possibility that any source (e.g., roommates) is overlooked. In contrast, the index of exposure in social settings is highly subjective, and persons more habituated to passive smoke may report a given exposure as less severe than persons less accustomed to smoke, thus creating a negative bias. The proportion of controls classified as exposed to ETS is 80%, which is high in comparison to other studies. This suggests that some exposed controls may have only minor exposure to ETS, making detection of an association (if present) less likely. Unlike almost every other ETS study, males and females are combined in the analysis and only the joint results are reported. Because there are 45 (146) pairs of males (females), the sample sizes are sufficient to warrant reporting odds ratios separately by sex and to test the hypothesis of no difference due to gender.

Lung cancer odds ratios for adulthood, lifetime, and spousal smoking are consistently well below one for low ETS exposure relative to nonexposure, as if exposure had a protective effect. Thereafter, however, the odds ratios associated with increasing levels of exposure are suggestive of an upward trend in response. Although we would not dismiss the occurrence of this outcome as attributable to chance alone, it is consistent with the baseline lung cancer mortality rate in the control population simply being higher than that of the case population for reasons other than exposure to spousal smoking. A pervasive (systematic) negative bias linked with exposure could also produce such an effect. Both of these contingencies are speculative, however, because there is no evidence in the article to support either, aside from the outcome of the data. Further fueling the speculation, however, are the markedly lower odds ratios obtained from surrogate responses,

indicative of some source of bias acting unequally on proxy and nonproxy sources. Also speculative is the idea that using predicted responses from a model that fits the data poorly might produce such an effect, but that level of detail is beyond the scope of most published articles, including this one. Some explanatory discussion by the authors on these issues, as well as *separation of the analyses by sex,* would enhance interpretation of results and facilitate comparison with results of other studies on females.

The authors' finding that exposure during childhood and adolescence appears to influence subsequent lung cancer risk more than exposure during adulthood raises some interesting possibilities. More time may be spent in proximity to a household smoker (particularly the mother), on average, in childhood than in adulthood. According to data presented by K.M. Cummings (Roswell Park Memorial Institute, Buffalo, NY) at the Science Advisory Board meeting on EPA's draft ETS report (U.S. EPA, 1990), on December 4-5, 1990, heavy childhood exposure is a better surrogate for total lifetime exposure than is spousal exposure. Also, early exposure may appear to become a risk, either due to a long latency period for lung cancer or, perhaps, due to increased susceptibility at an earlier age. The results suggesting an effect from early exposure but not from spousal smoking are more nearly atypical than reinforced by other studies, though, and the number of exposure sources considered raises the possibility that the strength of association seen for preadult exposure may be due to chance. However, after elimination of 78 pairs with incomplete marriage or household exposure data, the association persisted and was strengthened (OR = 2.59), arguing against chance as the major influence. It is unclear what role, if any, negative bias due to proxy respondents may have had in the nonspousal analyses.

In summary, the findings for preadult exposure are not readily attributable to chance or confounding, although some role of interviewer bias or unmeasured confounding factors such as diet cannot be ruled out. No association with lung cancer incidence is observed for spousal smoking. The authors conclude, however, that, spousal smoking aside, other sources of household ETS exposure support the conclusion that exposure to ETS can cause cancer. That conclusion is not unequivocal in our view. In general, the odds ratios (aside from preadulthood exposure) tend to be low but trend upward with exposure, exhibiting more of a patterned response than one might expect to see due to randomness. This is puzzling as there is no apparent source of bias and the study appears to have been conducted with considerable forethought and thoroughness. The only exception noted is the lack of separate analyses and comparisons of males and females. These concerns notwithstanding, the study is a useful addition to the literature on ETS exposure and lung cancer.

A.18. KABA

A.18.1. Author's Abstract

"Among 2,668 patients with newly diagnosed lung cancer interviewed between 1971 and 1980, 134 cases occurred in 'validated' nonsmokers. The proportion of nonsmokers among all cases was 1.9% (37 of 1,919) for men and 13.0% (97 of 749) for women, giving a sex ratio of 1:2.6. Kreyberg Type II (mainly adenocarcinoma) was more common among nonsmoking cases, especially women, than among all lung cancer cases. Comparison of cases with equal numbers of age-, sex-, race-, and hospital-matched nonsmoking controls showed no differences by religion, proportion of foreign-born, marital status, residence (urban/rural), alcohol consumption or Quetelet's index. Male cases tended to have higher proportions of professionals and to be more educated than controls. No differences in occupation or occupational exposure were seen in men. Among women, cases were more likely than controls to have worked in a textile-related job (relative risk = 3.10, 95% confidence interval 1.11-8.64), but significance of this finding is not clear. Preliminary data on exposure to passive inhalation of tobacco smoke, available for a subset of cases and controls, showed no differences except for more frequent exposure among male cases than controls to sidestream tobacco smoke at work. The need for more complete information on exposure to secondhand tobacco smoke is discussed."

A.18.2. Study Description

In 1969, the American Health Foundation began interviewing newly diagnosed lung cancer patients with cancer at sites potentially related to tobacco use for a case-control study that is still ongoing (Wynder and Stellman, 1977). The current article considers the data on lung cancer in nonsmokers alone collected from newly diagnosed lung cancer patients between 1971 and 1980. Several factors are of interest: histology, demographic factors, residence, Quetelet's index, alcohol consumption, previous diseases, occupation and occupational exposures, and ETS exposure. The number of nonsmokers among the cases is small, so the authors consider the results to be preliminary.

The study from which the data on lung cancers in nonsmokers are extracted is a very large effort that includes tobacco-related cancers at multiple organ sites and includes smokers as well as nonsmokers. The cases are from approximately 20 hospitals in 8 U.S. cities (about one-third from New York City). With reference to the lung cancer cases in that study, histologic type of lung cancer was determined from pathology reports and discharge summaries. Secondary lung cancer cases were excluded. Controls consist of hospital patients with diseases unrelated to tobacco use who were pair-matched with cases on hospital, age (within 5 years), sex, race (with five

exceptions), date of interview (within 2 years), and nonsmoking status. Cases appear to be incident, and control sampling is density. All subjects were interviewed while patients were in the hospital. The questionnaire for the interviews was expanded in 1976. Questions on exposure to ETS were not included, however, until an addendum to the questionnaire in 1978, which was then modified in 1979.

The term "nonsmoker" applies to subjects who have smoked less than one cigarette, pipe, or cigar per day for a year. The term "never-smoker" is used interchangeably. Independent of the intended definition, however, subjects whose hospital charts indicated any record of smoking, even in the remote past, were excluded from the nonsmoker classification. ETS subjects include 53 (25) females (males), after combined attrition of 22 (9 without primary lung cancer and 13 with a record of smoking). The age distribution of the female cases (controls) is as follows: age less than 50, 12 (15); age 50 to 59, 26 (24); age 60 to 69, 29 (34); age 70 or more, 30 (24). Histologic data on lung cancer type are given for female cases: squamous cell (16), adenocarcinoma (60), alveolar (12), large cell (4), and unspecified (5). The authors report that exposed cases did not differ from the unexposed cases in the distribution of histologic type.

A person is "ETS exposed" (1) at home, if currently exposed on a regular basis to family members who smoke, (2) at work, if currently exposed on a regular basis to tobacco smoke at work, and (3) to spousal smoke, if the spouse smokes. There are data on 53 cases and their controls for exposure at home and at work, but data on only 24 cases and 25 controls for spousal smoking. This is because of the change in the questionnaire from 1978 to 1979 and because spousal smoking was only applicable for women currently married. Because nonsmoking status was a variable for matching, the 53 pairs of cases and controls for analysis of exposure at home or at work are matched; the data for spousal smoking, however, are technically not matched. There is no indication at all of an association between ETS exposure and lung cancer for women from exposure at home, at work, or from spousal smoking. For ETS exposure at home, there are 16 out of 53 (exposed/total) cases and 17 out of 53 controls; for exposure at work, the figures are 26 out of 53 cases and 31 out of 53 controls; and for spousal smoking, the data are 13 out of 24 cases and 15 out of 25 controls. No statistical calculations are provided for females. From cur calculations, the odds ratio for spousal smoking is 0.79 (95% C.I. = 0.25-2.45). (Among male subjects, exposure to ETS in the workplace was slightly significant, $p = 0.05$, as reported in the article.) For other potential risk factors for lung cancer in women other than passive smoking, it was found that cases were more likely than controls to have worked in a textile-related job (OR = 3.1; 95% C.I. = 1.1-8.6), but the significance of the finding was not clear. It was also found that more female

cases had a history of pneumonia compared to controls, but no interpretation could be attached to the observation.

A.18.3. Addendum

Unpublished preliminary results of a study of ETS and lung cancer in never-smokers conducted at the American Health Foundation have been reported at two meetings—The American Public Health Association (APHA) 119th Annual Meeting, Atlanta, Georgia, November 10-14, 1991, and The Toxicology Forum, 1990 Annual Winter Meeting, Washington, D.C., February 19-21, 1990. A completed report for our review was not available at the cutoff date for inclusion in this document (personal communication with the first author, Dr. G.C. Kabat). Enclosed below is the abstract for the APHA meeting.

RISK FACTORS FOR LUNG CANCER IN LIFETIME NON-SMOKERS
Geoffrey C. Kabat, Ernst L. Wynder

Risk factors for lung cancer in lifetime non-smokers (NS) were assessed in a hospital-based case-control study carried out between 1983 and 1990. The study population consisted of 41 male and 69 female NS cases and 117 male and 187 female NS controls matched on age, race, hospital, and date of interview. Evidence of an effect of exposure to environmental tobacco smoke (ETS) was inconsistent. In males, there was no difference between cases and controls in reported exposure to ETS (yes/no) in childhood, in nonsignificant association with exposure in childhood (OR = 1.6, 95% C.I. 0.9-2.8), but no association with exposure in adulthood at home or at work. Male cases were somewhat more likely to have a smoking spouse (OR = 1.6, 95% C.I. 0.7-3.9), whereas there was no difference in females. Cases and controls did not differ in reporting a history of previous respiratory diseases. Female cases were more likely to report a history of radiation treatment (OR = 4.3 95% C.I. 1.5-12.3). In females, but not in males, a significant inverse association was observed between body mass index (based on self-reported weight 5 years prior to diagnosis) and lung cancer risk.

A.18.4. Comments

Although the study contains more than 2,600 patients, only a small number of nonsmokers are available because questions about ETS exposure were not included in the interview until 1978 and the questions were changed in 1979. It is not clear just how the questionnaire was changed, although the general tenor of the article suggests care in study planning and execution. The design for the larger study from which the ETS data are taken is pair-matched on numerous factors of potential interest, including "nonsmoking status," which contributes favorably to the analysis of ETS data alone. Cases with secondary tumors were excluded, histological type was considered, and all subjects were personally interviewed. It appears that only the currently married females were included in the question regarding exposure to spousal smoke, which

alleviates the need to make some approximating assumptions regarding exposure of widows, singles, and so forth.

Two potential concerns about the analysis of ETS subjects have to do with the definition of "ETS exposure" and "nonsmoker." It is noted that duration of smoking was comparable in cases and controls, but interview questions regarding exposure to ETS refer only to current exposure (this is not explicit in the article but was confirmed by the first author). Also, this measure of exposure has no units (e.g., number of cigarettes per day or pack-years smoked by spouse), which might leave the question less subjective and perhaps help to dichotomize on ETS exposure more sharply. Because lung cancer may have a latency period of 20 years or so, exposure in the past, both in terms of duration and intensity, may be more meaningful than recent exposure. With regard to the definition of nonsmoker, the requirement is less rigid than is often imposed. Ever-smokers are included provided they did not smoke more than the equivalent of 1 cigarette per day for 1 year (about 18 packs). Smoking may seriously confound ETS exposure, and it is difficult to know what constitutes a "negligible" level of past smoking.

One of the factors of interest to the investigators is occupation, so cases and controls were not matched on that variable. For ETS exposure, occupation could be a potential confounding factor. Among females, the controls contain a higher percentage of professional and skilled workers than do the cases (47 to 25), and a lower percentage of housewives (41 to 50). Some differences are also apparent in religious preference between cases and controls that may bear some influence through lifestyle or dietary practices. Variables such as these may need to be taken into account in an adjusted analysis when more data become available.

As noted previously, this article is presented as a preliminary report, and it should be interpreted in that light. The data set on ETS subjects is small. We expressed some reservations about the operational meaning of "nonsmoker" and "ETS exposed," both of which could be more strict. Nonsmokers may have a light history of smoking; exposed nonsmokers may have very little history of exposure. Both factors may be sources of bias, the second one toward the null hypothesis of no effect, and the first one possibly in either direction. This study contributes some useful evidence for the epidemiologic evaluation of whether ETS poses a detectable lung cancer risk, but the potential for bias and the uncertainty due to small sample size could be influential.

A.19. KALA

A.19.1. Author's Abstract

"A case-control study was undertaken in Athens to explore the role of passive smoking and diet in lung cancer, by histologic type, in non-smoking women. Among 160 women with lung

cancer admitted to one of seven major hospitals in Greater Athens between 1987 and 1989, 154 were interviewed in person; of those interviewed, 91 were life-long non-smokers. Among 160 identified controls with fractures or other orthopedic conditions, 145 were interviewed in person; of those interviewed 120 were life-long non-smokers. Marriage of a non-smoking woman to a smoker was associated with a relative risk for lung cancer of 2.1 (95% confidence interval [CI] 1.1 — 4.1); number of cigarettes smoked daily by the husband and years of exposure to husband's smoking were positively, but not significantly, related to lung cancer risk. There was no evidence of any association with exposure to smoking of other household members, and the association with exposure to passive smoking at work was small and not statistically significant. Dietary data collected through a semi-quantitative food-frequency questionnaire indicated that high consumption of fruits was inversely related to the risk of lung cancer (the relative risk between extreme quartiles was 0.27 (CI 0.10 — 0.74). Neither vegetables nor any other food group had an additional protective effect; furthermore, the apparent protective effect of vegetables was not due to carotenoid vitamin A content and was only partly explained in terms of vitamin C. The associations of lung cancer risk with passive smoking and reduced fruit intake were independent and did not confound each other. Passive smoking was associated with an increase of the risk of all histologic types of cancer, although the elevation was more modest for adenocarcinoma."

A.19.2. Study Description

This study was undertaken in Athens, Greece, in 1987-89. It sought to explore the role of passive smoking and diet in the causation of lung cancer in nonsmoking women. All data used in the study were collected specifically for that purpose.

Cases are never-smoking women hospitalized in one of seven Greater Athens area hospitals during an 18-month period of 1987-89 with a definite diagnosis of lung cancer from histologic, cytologic, or bronchoscopic exam. Controls were selected from female never-smoking patients in the orthopedic ward of the same seven hospitals and an orthopedic hospital. A control was interviewed within 1 week of a corresponding case, thus essentially density-sampled but otherwise unmatched. Cases were not specifically restricted to incident cancers. All subjects were interviewed face-to-face by one of five trained interviewers; interviews were apparently unblinded. A total of 160 lung cancer cases and an equal number of controls were initially identified; 6 cases and 12 controls were too ill to interview, whereas 3 controls and no cases refused to participate. After exclusion of smokers, 91 cases and 120 controls remained. The age distributions of the cases and controls are very similar: for cases and controls, 16.5% (14.2%) were less than 50 years of age, 19.8 (18.3%) were 50 to 59, 29.7 (25.8%) were 60 to 69, and 34.1 (41.7%)

were 70 or older. Current residence, level of education, occupation (housewife vs. other) and marital status were also similarly distributed between cases and controls. Case diagnosis was established by histology (48%), cytology (38%), or bronchoscopy (14%), with exclusion of cancers diagnosed as secondary.

Persons reportedly smoking fewer than 100 cigarettes in their lifetime are classified as nonsmokers. No mention is made of pipe or cigar smoking. Several different sources of ETS exposure are considered: husbands who smoke quantified in terms of years exposed and average number of cigarettes smoked per day; household members *other* than husbands who smoke, quantified by the sum of years exposed to each smoker; and coworkers who smoke, measured by the number of smokers sharing the "same closed space" as the subject. Presumably childhood exposure is included in the household exposure assessment. For spousal smoking, single women are considered unexposed, whereas exposure of widowed or divorced women is based on their married period. No attempts to verify exposure are mentioned.

For analysis of husband's smoking based on cigarettes per day, 64 out of 90 (exposed/total) cases and 70 out of 116 controls gives a crude odds ratio of 1.6 for 90 cases and 116 controls; 64 cases and 70 controls were exposed. The authors present results stratified by four exposure categories, which indicate no significant association ($p = 0.16$). Crude data for husband's smoking stratified by five levels of smoking duration (never, < 20, 20-29, 30-39, and 40+ years) yield a marginally significant increase in association with increasing duration ($p = 0.07$), with odds ratios of 1.0, 1.3, 1.3, 2.0, and 1.9, respectively. No statistically significant association was noted for ETS exposure from other household members ($p = 0.60$) or for exposure at work ($p = 0.13$), but the crude odds ratios for these exposures were 1.41 and 1.39, respectively. Stratification by level of intake for each of 16 food and nutrient groups yielded a significant negative (favorable) association with cereals ($p = 0.04$) and a possible association with fruits ($p = 0.11$).

Multiple logistic regression was then used to adjust results for age, education, and interviewer. An adjusted relative risk estimate of 1.92 (95% C.I. = 1.02-3.59) was obtained for marriage to a smoker. After adjustment, trends for estimated lung cancer risk showed an increase with duration of exposure (average 16% per 10 years) and packs per day (6% per pack), but these were not statistically significant. No trend was observed for ETS in the household or workplace. Adjustment for other sources of air pollution had no effect on the analyses. Adjustment of dietary analyses for age, education, interviewer, and total energy intake indicated a significant decrease in estimated risk between highest and lowest quartiles of consumption of fruit ($RR = 0.33$; $p = 0.02$) and a nearly significant increase with consumption of retinol ($RR = 1.31$; $p = 0.06$), whereas beta carotene ($RR = 1.01$) and other dietary factors had no significant effect.

Adding fruit consumption to the model for passive smoking increased the adjusted relative risk for husband's smoking slightly, from 1.92 to 2.11. Stratification by lung cancer cell type yielded somewhat lower adjusted estimated relative risks for adenocarcinoma (2.04) than for squamous, small, and large cell cancer combined (2.58). No adjusted results were presented for other household or workplace exposure.

The authors' conclusion is best reflected in their abstract (shown in full above). Marriage of a nonsmoking woman to a smoker was associated with a relative risk for lung cancer of 2.1. Number of cigarettes smoked daily by the husband and years of exposure to husband's smoking were positively, but not significantly, related to lung cancer risk. There was no evidence of any association with exposure to smoking of other household members, and the association with exposure to passive smoking at work was small and not statistically significant. Dietary data indicated that high consumption of fruits was inversely related to the risk of lung cancer. Neither vegetables nor any other food group had an additional protective effect. The associations of lung cancer risk with passive smoking and reduced fruit intake were independent and did not confound each other. Passive smoking was associated with an increase of the risk of all histologic types of cancer, although the elevation was more modest for adenocarcinoma.

It is noted that these findings are compatible with the relatively low incidence of lung cancer in the Greek population—a population with the highest per capita tobacco consumption in the world, but with a very high fruit consumption as well.

A.19.3. Comments

This study was generally well designed and executed. Set up specifically to address passive smoking and diet as etiological factors in lung cancer, it includes sufficient numbers of nonsmoking women to produce substantive results. Interviews were face-to-face and no proxies were used, enhancing accuracy and comparability of responses, whereas the very low rate of refusal minimizes potential bias due to volunteer selection. Cases and controls were very similar demographically, were drawn from most of the same hospitals, and were matched temporally on time of interview, so comparability seems high. Furthermore, the study hospitals' patient population accounts for the majority of lung cancer and trauma patients seen in the Athens area, enhancing generalizability of results. Most lung cancers were histologically or cytologically confirmed, reducing chances for misclassification of disease status.

On the debit side, the apparently unblinded interviews could have been biased (although what can be accomplished toward that end is limited). Adjustment for interviewer in the analyses did not affect the results, however, and it is unlikely that all interviewers would share the same

bias. Determination of what constitutes workplace exposure is vague, and childhood exposure is not clearly differentiated from adult household exposure; these were notably the passive smoking categories, which showed the least association with lung cancer. ETS exposure in the workplace is analyzed with regard to trend (Table 2), with levels of exposure represented by "housewife" (zero exposure), "minimal," and "some," resulting in a p value of 0.13. Perhaps correctly, the authors cautiously note the evidence that ETS exposure is associated with increased risk (referring to Table 2 in general, not just exposure at work) but indicate that the differences are not large enough to be interpretable without controlling for confounding effects. An analysis of exposed versus unexposed for the workplace may have been useful, especially an adjusted analysis. Our calculation of the crude odds ratio for a comparison of "minimal" and "some" exposure at work is 1.7, which is suggestive.

Methodological rigor and thoroughness are particularly evident in the treatment of potential sources of confounding. Despite the demographic similarity of cases and controls, the key demographic variables of age and education were nevertheless controlled for in the analyses, along with interviewer identity. Air pollution, total energy intake, and other dietary factors were also examined as potential confounders, and the impact of cancer type was evaluated. An association of husband's smoking with lung cancer yielding an odds ratio of around 2 persisted throughout. The authors claim to have taken special effort to exclude ex-smokers from misclassification as never-smokers, taking account of this potential source of upward bias. No discussion was found, however, of what measures were taken to control misclassification of former smokers as never-smokers, beyond interviewing subjects about current and former smoking habits.

In summary, this study presents evidence of a level- and duration-dependent association between husband's smoking and lung cancer in a well-defined and highly comparable group of Greek cases and controls. Positive but nonsignificant relationships with general home or workplace passive smoking were observed, and there are indications that additional analysis of workplace exposure may be worthwhile. No effect of air pollution was observed. With regard to dietary factors, the large number of potential factors considered raises the issue of multiple comparisons. Fruit consumption may be a significant factor, but further evidence is needed to firmly establish this, particularly in view of the number of dietary factors explored. Dietary factors, however, do not account for the results for ETS exposure in this study. The results regarding spousal smoking cannot be readily attributed to bias, and they provide good quantitative data on the issue of passive smoking and lung cancer. This well-conducted study makes a valuable contribution to the evidence on lung cancer and ETS exposure.

A.20. KATA

A.20.1. Author's Abstract

"It is becoming noticeable in Japan that with increased incidence of lung cancer, there has been an increase in pulmonary carcinoma in women. Active smoking by women is increasing, while concern over passive smoking has been intensifying, and the effect of passive smoking on carcinogenesis had become a social problem. Regarding this effect, immunological and public health reports have appeared in Japan, but there have been few clinical reports, and detailed analysis of patients has been inadequate. Lung cancer presents a variegated histological picture, and presumably there are different carcinogenic factors for different histological types, although there have also been few reports on this subject. The effect of passive smoking probably varies depending on the regional environment and custom, and these factors should also be analyzed and included in the investigation. The present report describes our findings regarding the effects of smoking and familial aggregation of cancer in cases of pulmonary carcinoma in women."

A.20.2. Study Description

This study was undertaken in the Nara Prefecture, Japan, to investigate the effects of smoking and familial aggregation of cancer in cases of pulmonary carcinoma in women. Active smokers are included in the study, from which the nonsmokers are drawn for analysis. Matching is retained, however, in the nonsmokers.

For the whole study, subjects were drawn from a hospital (presumably the Nara Prefecture Medical University Hospital) during an unspecified period of time. Cases are female patients with histologically diagnosed lung cancer; controls are female patients with "non-malignant" disease, matched 2 to 1 with cases on age plus or minus 2 years. It is not clear if only incident cases were used and if controls were density sampled. Case diagnoses were obtained from histological exam results, whereas control diagnoses were presumably from medical charts. Other information was collected from apparently unblinded "questioning," with an unspecified degree of reliance on proxy responses from family members.

A total of 25 cases and 50 controls are included in the study; no information on refusals is provided. Exclusion of active smokers leaves only 17 cases and, with retention of 1:1 matching, 17 controls. Mean ages for the total study population are 67.5 ± 8.8 years (67.6 ± 8.5 years) for cases (controls). The age distribution of ETS subjects is not discussed. Nonsmokers are defined by exclusion of "active smokers," with no delineation between former and current smokers. ETS exposure is defined as exposure to smoking more or less daily through living with a smoker. Three periods of ETS exposure are considered: current, past, and childhood, the last for those

"exposed since early childhood." Clearly these types are not mutually exclusive, although current sources of exposure are omitted from the "past" exposure category, even if present for a long time.

ETS exposure is quantified as cigarettes per day smoked times number of years. No mention is make of cigar or pipe smoking, nor of checks on exposure data. No distinction is made regarding marital status. Tumors occurring among current passive smokers were mostly adenocarcinomas (13/17), the remainder (4/17) being squamous or small cell cancers. Airway proximity was not specified. Excluding active smokers, all 17 cases were current passive smokers, compared to 14 out of 17 controls, for an odds ratio of 1.2, whereas past passive smoking characterized 16 of 17 cases and 17 of 17 controls, for an odds ratio of 0.9 (these odds ratios reflect the substitution of 0.5 for 0 in the exposure categories in which no subjects fall). Childhood passive smoking was reported in 13 of 15 cases and 7 of 15 controls (apparently all those for whom information was available), for an odds ratio of 7.4 ($p < 0.1$). None of the passive smoking odds ratios was statistically significant at the 5% level. No definite conclusion can be drawn from the present study, but there is a suggestion that passive smoking is associated with development of lung cancer in the Nara region. The effect of passive smoking that continued to the present time was especially marked, particularly in squamous cell carcinoma and small cell carcinoma. With adenocarcinoma, an effect of passive smoking in the past is suspected. Along with passive smoking, the association of some intrinsic factor (genetic tendency) to varying degrees in the different histologic types of lung cancer in women, especially in adenocarcinoma, is apparent.

A.20.3. Comments

The histological diagnosis of all cases, in combination with the apparent involvement of the researchers in the diagnoses, virtually eliminates the potential pitfall of misclassification of lung cancer cases. It also allows specific breakdowns by cell type. With regard to passive smoking, however, limitations related to exclusion of active smokers greatly reduced the study's potential.

In their initial analyses, the authors investigate passive smoking without excluding or stratifying on active smoking and report statistically significant associations with lung cancer and combined effects with family history of cancer. This is not a meaningful analysis, because the effects of active and passive smoking cannot be separated and because passive smoke exposure probably correlates strongly with extent of active smoking. Excluding active smokers greatly reduces the available numbers of matched subjects and, in combination with the very high exposure prevalence among qualifying controls, makes the differences between cases and controls

highly unstable for all comparisons except for that of childhood exposure. Even here, with an estimated relative risk of 7.4, the results do not reach the 5% level of statistical significance, notwithstanding the problem of multiple comparisons. This does not deter the authors from attempting cell-type-specific analyses, but these too fail to yield significant results. The extraordinarily high proportion of exposed present and past passive smoking controls is apparently a fluke, because the proportion is not as high in the total control subject population (or childhood passive smoking controls). Nevertheless, exposure was very common among controls. This indicates that the exposure criteria may be too lax or, alternatively, that the control population included a substantial proportion of persons with smoking-related diseases (controls being only stipulated not to have malignant disease).

In light of the minimal utility of the study's passive smoking analyses, detailed consideration of design strengths and weaknesses is unwarranted. Major points not already mentioned relate to information ascertainment and confounding. Interviews were apparently unblinded and, especially if conducted by the authors themselves, may thus have been biased toward uncovering exposure among cases (although the high prevalence of exposure among controls as well as cases argues against this). Furthermore, the extent of proxy interviews, potentially decreasing accuracy of exposure assessment, is unclear.

All subjects are female and, although results are not age adjusted, matching on age was retained for all analyses. No other potential confounders except family history of cancer were considered, probably due to limited subject numbers, because much information on potential confounders was collected. Moreover, family history was considered only in the nonmeaningful analyses, which did not differentiate active and passive smokers. Thus, although the problems with numbers and exposure misclassification probably reduced the study's ability to detect whether an association exists, information bias and confounding could have biased results either up or down.

In summary, this study's data are consistent with an association of passive smoking, particularly childhood exposure, with lung cancer, but the results are too unstable and subject to potential bias to carry much weight, and the quantitative results must be viewed with extreme caution.

A.21. KOO

A.21.1. Author's Abstract

"Lifetime exposures to environmental tobacco smoke from the home or workplace for 88 "never-smoked" female lung cancer patients and 137 "never-smoked" district controls were

estimated in Hong Kong to assess the possible causal relationship of passive smoking to lung cancer risk. When relative risks based on the husband's smoking habits, or lifetime estimates of total years, total hours, mean hours/day, or total cigarettes/day, or earlier age of initial exposure, were combined with years of exposure, there were no apparent increases in relative risk. However, when the data were segregated by histological type and location of the primary tumor, it was seen that peripheral tumors in the middle or lower lobes (or less strongly, squamous or small-cell tumors in the middle of lower lobes) had increasing relative risks that might indicate some association with passive smoking exposure."

A.21.2. Study Description

This study, the second of four from Hong Kong, is based on a secondary data set of reported female never-smokers. The parent study from which the data on ETS subjects was drawn includes ever-smokers in a matched case-control study of 200 cases and 200 controls (Koo et al., 1984; also see Koo et al., 1983). Its objective is to assess the role of passive smoking as a potential etiological factor in the high incidence rate of lung cancer among Chinese females in Hong Kong. The current article emphasizes the quantitation of lifetime ETS exposure and the histological profile of lung cancer in exposed never-smokers.

In the parent study, cases are from the wards or outpatient departments of eight hospitals in Hong Kong during 1981-83. Controls are healthy subjects from the community, matched on age (within 5 years), district of residence, and type of housing (public or private). The cases are incident, and control sampling is density. Attrition due to selection or follow-up totals 26 (8 too ill to interview and 18 with secondary lung cancers), leaving 200 cases for interview. Face-to-face interviews of 1.5 to 2 hours were conducted directly with cases and controls. There was no restriction of cases by cell type of lung cancer. The ETS subjects extracted from the parent study include 88 cases and 137 controls. Of the 88 cases, 83 were confirmed by histology and 5 were "confirmed malignant." The number of squamous cell and small cell cases combined is 32 (23 ETS exposed; 72%); the corresponding figure for adenocarcinoma and large cell combined is 44 (31 ETS exposed; 70%); 12 cases are of another cell type, or otherwise unspecified. For the 86 cases with available information, tumors were centrally located in 37 (25 ETS exposed; 67%) and peripherally in 46 (34 ETS exposed; 74%).

The term "never-smoker" applies to persons who have smoked a total of fewer than 20 cigarettes. Interview questions regarding exposure to ETS include cigarette and cigar smoking in the home during childhood, by the spouse and other cohabitants in adulthood, and workplace exposure. "ETS exposed" is technically used in several ways. For the comparison of exposed with

unexposed ever-marrieds, it means the husband ever smoked in the wife's presence. For measures of exposure in terms of duration or rate (e.g., total years, hours/day, total hours, and cig./day), there is some variation. For example, total years of exposure is derived by adding the years during which tobacco exposure occurred in the home or workplace. The total hours of exposure are calculated by multiplying the average hours per day of exposure by the years of exposure from each household smoker, or the amount of exposure at each workplace. The mean hours per day of exposure are found by adding the hours per day of home and workplace exposures and dividing this figure by the age of the subject. This figure is intended to approximate the average number of hours of exposure per day experienced by the subject, over her lifetime. Cumulative exposure is estimated by the total cigarettes smoked by family members, weighted by years of exposure.

When data are analyzed on the simple basis of whether a husband ever smoked in the presence of the wife, the crude and adjusted odds ratios are 1.55 (95% C.I. = 0.94-3.08) and 1.64 (95% C.I. = 0.87-3.09), respectively. The crude analysis applies to ever-marrieds only, which excludes three subjects. An adjusted analysis uses cigarettes per day smoked by the husband as the measure of ETS exposure. Conditional logistic regression was applied with stratification on district of residence and housing type (public/private); model parameters were included for age, family history of lung cancer (yes/no), number of live births, and number of years since exposure at home or in the workplace.

The crude and adjusted methods give very similar odds ratios and confidence intervals, but the tests for trend differ substantially. The test for trend on the crude data is based on the Mantel-Haenszel test, using midpoints of the intervals for cigarettes per day smoked by the husband; the significance value is $p = 0.10$. The p value for trend in the adjusted analysis is 0.32. For analysis of data by other measures of exposure, as described above, the estimated odds ratio ranges between 1.0 and 4.1 across the three levels of the various measures of ETS exposure for both the analyses of the crude data and the adjusted analyses by conditional logistic regression, with two exceptions from analysis of the crude data for hours per day of exposure. The results are not statistically significant in most cases, because the sample sizes at each exposure level are small. The dose-response patterns observed are clearly sensitive to the measure of ETS exposure used, with several exhibiting an apparent peak at a low exposure level. Although the authors acknowledge that it was troubling to find the lack of a response pattern, no further explanation is given.

The authors did not detect a significant trend in the crude or adjusted odds ratio for the four lifetime measures of passive smoking (total years, hours, mean hours/day, cig./day). Although the odds ratio for the intermediate level exposures of hours per day and cigarettes per

day was significant, the odds ratio at the highest levels of exposure for these two variables fell to a nonsignificant 1.0 to 1.2. In fact, the odds ratio for the highest exposure levels for three out of the four measurements were below all of those with lower exposures and ranged from a very weak 1.0 to 1.4. On the other hand, most of the crude and adjusted odds ratios were greater than 1.0. Measurements based on increasing intensity of exposure, defined as increasing years (or hours, or cig./day) by mean hours per day of exposure, also did not indicate a dose-response relationship. The analysis of total years of exposure with age of exposure did not suggest that earlier age of initial exposure and increasing years of exposure led to higher odds ratios.

It is concluded that when the lung tumors were segregated by histological type and location, the resulting analyses showed that peripheral tumors in the middle or lower lobes, and squamous or small cell tumors in the same lobes, exhibited better odds ratio patterns for passive smoking in terms of consistency, strength, and dose-response. The odds ratio for total years, hours, and hours per day measurements of squamous and small cell lung tumors indicated consistently elevated risks with increasing exposure. This pattern was not found for any of the adjusted odds ratios for adenocarcinoma or large cell lung cancers.

The cases are divided into two groups histologically, those with squamous cell or small cell tumors, and those with adenocarcinoma or large cell malignancies. Although none of the crude or adjusted analyses are found to be significant, it is concluded that an observed dose-response pattern seems to be more apparent in the squamous or small cell group. With regard to tumor location, some evidence suggests that peripheral tumors in the middle or lower lobes may be more common in passive smokers.

A.21.3. Comments

As described above, the data employed in the current study were taken from a larger retrospective study of female lung cancer in Hong Kong (Koo et al., 1984) that matched 200 cases and controls on age, district of residence and housing type (private or public, an indication of socioeconomic status). Attention to detail and accuracy is evident in most aspects of the parent study. In particular, considerable effort was put into attempting to ascertain a better quantitative measure of exposure than used in preceding studies of ETS. Records were apparently verified to the extent possible to cross-check the accuracy of information collected, cancers were verified histologically, and analyses investigated questions related to the histological types and sites of tumors that may be related to passive smoking.

The never-smokers from the parent study, 88 cases and 137 controls, compose the secondary data set on which the current article is based. The matching of the subjects, of course,

is no longer assured, leaving the comparability of the two groups uncertain. In addition, 60 (27%) of the subjects are widows, with no information provided on the distribution between cases and controls. Because spousal smoking is typically the variable on which ETS exposure pivots, this may have some bearing on the response. An adjustment is made in some analyses for years since exposure to cigarette smoke ceased, but no information is provided to describe or support the assumptions used to do that.

Some factors in the study itself may be contributing to the variable dose-response patterns. First, the number of ETS subjects is fairly small. When the subjects are classified into finer categories of exposure, the statistical variability is greatly increased (total cases and controls is below 60, on average). Second, questionable measurements of ETS may be causing some distortion. For instance, in the calculation of total years and total hours of ETS exposure, the years and hours were not added for simultaneous exposure to more than one smoker or for concurrent exposure in the home and workplace. Pipe smoking and the cigarette consumption levels of coworkers were excluded from the weighted average of the total cigarettes per day smoked by each household member. Additionally, the mean hours per day of exposure were derived by adding the hours per day of home and workplace exposures and dividing this figure by the *age* of the subjects. Thus, measurement appears to be based on the assumption that never-smoking women were exposed to ETS evenly throughout their lives (the authors claim that only subjects were used for which the exposure remained relatively regular during the lifetime, although no mention was found of cases being omitted because of failure to satisfy this criterion). Even if this assumption were valid, childhood and adulthood exposures are mixed as if the effects of exposure are interchangeable. Interestingly, differences between exposure in childhood and adulthood is one of the questions addressed in the article.

Although the objective is worthy, the attempt to quantitate exposure more precisely than previous studies appears to obscure more than to clarify. Assumptions are not made very explicit and their potential implications are not addressed well, which leaves some uneasiness about the conclusions. The authors have published at least three articles before this study that have some bearing on passive smoking and lung cancer, but their results are not discussed in the current study, even when the data analyzed are from the same source (Koo et al., 1983; Koo et al., 1984; Koo et al., 1985). Those articles, one of which describes the parent study (the 1984 citation), appear to reach somewhat different conclusions from this study regarding the predominance of histological type associated with passive smoking. Putting the current study's conclusions within the context of related prior work would enhance their clarity and interpretation.

Considering the reservations described above, the suggestion that the evidence indicates some association of passive smoking with the *location* of tumors is an overinterpretation of the data. A weaker conclusion is warranted, namely, that ETS exposure is associated with increased lung cancer incidence. What may be of most value in this study is the analysis based on the dichotomous classification of cases and controls as exposed or unexposed based on spousal smoking. Two concerns, however, will be reiterated. The ETS data are taken from a larger study not matched on smoking status, so they are unmatched. The study includes 80 widows, without mention of their distribution between cases and controls. In the adjusted analysis, an attempt is made to take into account the number of years since last exposure, which would require some assumption regarding the change of risk relative to cessation of exposure. Both of these concerns are mitigated, however, by the similarity of the odds ratios and confidence intervals for the unadjusted and adjusted analyses. The care and thoroughness of the study in general make the results on the odds ratio for exposure to spousal smoke a useful contribution for evaluation with other study outcomes.

A.22. LAMT

A.22.1. Author's Abstract

"In a case control study in Hong Kong, 445 cases of Chinese female lung cancer patients all confirmed pathologically were compared with 445 Chinese female healthy neighborhood controls matched for age. The predominant histological type was adenocarcinoma (47.2%). The relative risk (RR) in ever-smokers was 3.81 ($P<0.001$, 95% CI = 2.86, 5.08). The RRs were statistically significantly raised for all major cell types with significant trends between RR and amount of tobacco smoked daily. Among never smoking women, RR for passive smoking due to a smoking husband was 1.65 ($P<0.01$, 95% CI=1.16, 2.35), with a significant trend between RR and amount smoked by daily by the husband. When broken down by cell types the numbers were substantial only for adenocarcinoma (RR=2.12, $P<0.01$, 95% CI=1.32, 3.39) with a significant trend between RR and amount smoked daily by the husband. The results suggest that passive smoking is a risk factor for lung cancer, particularly adenocarcinoma in Hong Kong Chinese women who never smoked."

A.22.2. Study Description

This hospital-based case-control study was conducted in Hong Kong in 1983-86, to investigate whether smoking is a major risk factor for lung cancer in Hong Kong Chinese women and, if so, to determine the relationship between smoking and the histological types of lung

cancer. Both active and passive smoking are of interest. The ETS subjects constitute only a subset of the whole study, because it includes active smokers.

Eligible cases for the whole study are the 445 female patients with pathology-verified lung cancer admitted into eight large hospitals in Hong Kong during 1983-86. Cases were interviewed in person. Only a few eligible patients declined or were too ill to cooperate. An equal number of healthy neighborhood controls were identified and interviewed by density sampling. Controls were matched to cases on sex, age ($\pm$ 5 years), and place of residence. The cases and controls include both never-smokers and ever-smokers, but smoking status was not used in matching. "Never-smoker" means a person who never smoked as much as one cigarette per day, or its equivalent, for as long as 1 year.

A woman is "ETS exposed" if her husband smoked for at least 1 year while they lived together. If the husband was an ever-smoker, information on the type of tobacco and amount usually smoked per day by the husband and the duration of exposure was obtained. No information was collected on ETS exposure from other household members' smoking or smokers at work. Single (never married) women were classified as nonexposed (6.8% and 5.2% in cases and controls, respectively). The treatment of widowed and divorced subjects is not explicitly addressed. Age and place of residence, as well as a series of other demographic variables, are similar between cases and controls.

The distribution of lung cancer by cell type in ETS cases is as follows: squamous cell, 12 out of 27 (number exposed/total); small cell, 6 out of 8; adenocarcinoma, 78 out of 131; large cell, 7 out of 9; and others or unspecified, 12 out of 24. The corresponding crude odds ratios and 95% confidence intervals are 0.85 (0.35-2.06), 3.00 (0.53-16.90), 2.12 (1.32-3.39), 3.11 (0.50-19.54), and 1.08 (0.41-2.82), respectively. The odds ratio for all cell types combined is 1.65 (1.16, 2.35), based on 115 out of 199 (exposed/total) cases and 152 out of 335 controls. The data for all cell types together, and for adenocarcinoma alone, are both significant at $p < 0.01$. No information is available on the airway proximity of tumors.

Trend tests were conducted for the amount smoked daily by the husband, categorized in terms of cigarettes as "nil," 1 to 10, 11 to 20, and 21 or more. The odds ratios in the three exposure categories are 2.18, 1.85, and 2.07, respectively, when all cell types are included. For adenocarcinoma alone, the corresponding odds ratios are slightly higher (2.46, 2.29, and 2.89). The dose-response relationship does not appear to increase between the lowest dose and the highest dose, but a test for trend is significant ($p < 0.01$ for all cell types and $p < 0.001$ for adenocarcinoma alone) when the "nil" group is included. No adjusted analyses are given.

The authors conclude that the significant trends observed between relative risk and amount smoked daily by husband, for all cell types combined and for adenocarcinoma alone supports the view that the observed association between ETS exposure and lung cancer is likely to be causal.

A.22.3. Comments

This study is the fourth of the Hong Kong epidemiologic inquiries into tobacco smoke as a possible etiological factor in the high rate of lung cancer, particularly adenocarcinoma, among women. Active smoking was included as well as passive smoking because the previous studies in Hong Kong were inconclusive. According to the authors, this led to the hypothesis that smoking is not a risk factor for adenocarcinoma in Hong Kong Chinese women. Matching of controls to cases was conducted for the whole study, including active smokers. It cannot be assumed, however, that the never-smokers alone, who constitute 45% of the cases and 76% of the controls, are matched.

Overall the study demonstrates care in planning and execution. The sample size of ETS subjects is moderately large, providing higher statistical power than the previous Hong Kong studies. All cases were pathologically confirmed as primary lung cancers, essentially eliminating the potential for error due to disease misclassification. Odds ratios were calculated by histological type for comparison. Cases and controls were interviewed personally, apparently with no proxy respondents and very few refusals, which reduces the potential for response bias. The exclusive use of incident cases helps to control potential selection bias, and density sampling of controls contributes to comparability of cases and controls. For the whole study, including smokers, healthy controls were matched to cases by sex, age, and neighborhood of residence. The mean and standard deviation of ages are nearly identical in cases and controls. According to the authors, a comparison by other demographic variables showed that, for the whole study, cases and controls were also comparable in place of birth, duration of stay in Hong Kong, level of education, marital status, and husband's occupation. Further attention to detail is evident in the clear definitions of "never-smoker" and "ETS exposure," essential to accurate classification of subjects for analysis and interpretation. Single women were treated as not exposed to husband's smoking, which could be a source of bias because these women may be exposed from other household members. This possibility was considered, however, because the article reports that similar results were obtained when single women were excluded.

In summary, the crude odds ratios vary between 2.1 and 3.1 for small cell carcinoma, adenocarcinoma, and large cell carcinoma, with adenocarcinoma significant at $p < 0.01$. The odds

ratios are consistently elevated at all three intensity levels of spousal smoking, varying between 1.8 and 2.9, with the odds ratio for adenocarcinoma alone somewhat higher than for all cell types combined. There is no apparent upward trend, however, from the lowest smoking intensity (1-10 cig./day) to the highest (21+ cig./day). These statistical results are ostensibly suggestive of an association between ETS exposure and lung cancer incidence, but they are based on only crude data with cases and controls unmatched, even on ages. Nor are statistical methods used that could adjust for matching variables, or other factors, in the data analysis (e.g., by stratification or logistic regression). Although this study was carefully conducted in most respects, the disregard for potential confounding effects leaves the authors' conclusion uncertain.

A.23. LAMW

(*Note:* This study is part of the thesis of LAM Wah Kit submitted to the University of Hong Kong for the M.D. degree in 1985, entitled "A Clinical and Epidemiological Study of Carcinoma in Hong Kong." The description given below is from Chapter 7 of the thesis only, entitled "Case-Control Study of Passive Smoking, Kerosene Stove Usage, and Home Incense Burning in Relation to Lung Cancer in Nonsmoking Females (1981-84)," which the author submitted in response to our request. The abstract below was prepared by the reviewers, since none was available from the author.)

A.23.1. Abstract

The study's objective is to investigate the hypothesis that an inhaled carcinogen may be related to the high incidence of centrally situated adenocarcinoma of the lung observed in nonsmoking female patients. Air pollution is probably not an important factor because it presumably affects both men and women. Most women in Hong Kong either stay at home or join the work force in commerce, services, or manufacturing, which are not associated with any known risk factor for lung cancer. Three etiological activities, all predominantly in the home, are considered in this study: passive smoking, kerosene stove cooking, and home incense burning. No evidence was found to implicate exposure to kerosene stove fumes or incense burning in centrally located adenocarcinoma. There is suggestive evidence of an association between ETS exposure from smoking husbands and occurrence of peripheral (but not central) adenocarcinoma. Why the location tends to be peripheral instead of central is speculative.

A.23.2. Study Description

(*Note:* The details of the study are not complete in the material provided. Some useful information, however, is available.)

The cases are all of the Chinese female patients admitted to the University Department of Medicine, Queen Mary Hospital, Hong Kong, between January 1981 and April 1984 with histologically and/or cytologically confirmed carcinoma of the lung of the four major cell types. Care was taken to exclude patients with secondary carcinoma of the lung; otherwise, all patients were included. The controls are Chinese female patients admitted to the orthopedic wards of the hospital in the period 1982-84, comparable to lung cancer patients in age and social class. Patients with pathological fractures due to smoking-related malignancies, or peripheral vascular disease-related orthopedic conditions were excluded.

Both cases and controls were patients of the third-class general wards, mostly from the lower income group. All subjects were interviewed in person. The questions covered dialect group, occupation, smoking habits, passive smoking, domestic cooking with kerosene, and home incense burning, in the form of a standardized questionnaire. For very ill patients, or for patients who spoke a dialect other than Cantonese or Mandarin, the next-of-kin was interviewed, with the patients as interpreter. The whole study, including active smokers, contains 161 cases and 185 controls, similar in age (median age is 67.5 [66] for cases [controls]), socioeconomic status (as measured by occupation and years of schooling), and recent residence. The author considered it unnecessary to stratify on these or any other variables.

The ETS subjects consist of 75 (144) cases (controls), including 16 (14) never-married cases (controls). The distribution of cases by cancer cell type is as follows: squamous cell (7), small cell (3), large cell (5), and adenocarcinoma (60). Questions related to ETS exposure include details on each smoker in the home (husband, others, mother, and father), amount smoked per day, hours of ETS exposure per day, and number of years smoked. Information about exposure in the workplace includes size of the workplace, number of coworkers who smoke, exposure time/day, and number of years of exposure at work.

Only the data for adenocarcinoma, the predominant cell type observed and the pathogenesis of interest, are analyzed. The number of cases is 37 out of 60 (exposed/total), and the number of controls is 64 out of 144, where ETS exposure refers to spousal smoking. The odds ratio (calculated by the reviewers) is 2.01 (95% C.I. = 1.09-3.72). The author divides the cases by location according to airway proximity, with 18 out of 32 (exposed/total) located centrally and 19 out of 28 in peripheral regions. The respective risk ratios are 1.61 and 2.64. Two tests were conducted for significance, including the Bayesian risk ratio analysis and a test of the slope for

the exposure parameter in a simple logistic regression model. The significance levels are 0.11 and 0.19, respectively, for the central location, and 0.01 and 0.02, respectively, for peripheral tumors. The test results differ widely for total passive smoking (home or workplace). For the central location, the respective significance levels are 0.09 and 0.3; for peripheral locations, the corresponding values are 0.03 and 0.15. It is suggested that the different outcomes for the two tests applied to total passive smoking may be due to a nonlinear logistic dose-response curve or to errors in assessing the level of exposure due to incomplete information. The apparent association between passive smoking and peripheral adenocarcinoma (and not central tumors) in the cases was unexpected. Based on the available raw data, exposure to a smoking spouse, cohabitant, and/or coworker is associated with an odds ratio of 2.51 (95% C.I. = 1.34-4.67) for all cell types combined. The author concludes that there is a suggestion of passive smoking associated with peripheral adenocarcinoma, particularly passive smoking attributable to smoking husbands. Kerosene and incense burning were not found to be associated with adenocarcinoma, either central or peripheral.

A.23.3. Comments

Cases and controls appear to be comparable in age, socioeconomic status, and recent residence for the whole study (including active smokers), although the study design is not matched on these or other variables. Some discrepancies between cases and controls are apparent, however, such as a higher percentage of cases than controls working outside the home (41% compared to 28%). The figures for nonsmokers alone (i.e., the ETS subjects) are not given, so comparability is uncertain for analysis of ETS exposure. Care has been taken to include only primary lung cancer patients among the cases, essentially eliminating this potential source of bias. Subjects were personally interviewed, with apparently only a small number of proxy respondents required, although no figure is given. The interviews were apparently not blinded, but that may have not been feasible considering the nature of the questions asked and the use of noncancer patients as controls. Considerable attention is given to histological type of cancer and the location in terms of airway proximity.

The author is particularly interested in the etiology of adenocarcinoma and focuses discussion on the adenocarcinoma cases to the exclusion of others. Although the raw data pertaining to other cell types are tabulated, more attention to those types in the analyses would have been useful. The adenocarcinoma cases are categorized further by central and peripheral location, which are analyzed separately. Again, a combined analysis would be useful (the reviewers calculated the crude odds ratio for the combined data, which is given above). Although

logistic regression is employed as one of the two statistical tools for analysis, factors that may differ between cases and controls are not included. Potential confounding variables need to be controlled for, by logistic regression, poststratification, or otherwise. To claim that cases and controls are similar in potential confounding characteristics does not alleviate the need to adjust for them in the analysis, particularly when the ETS data are a subset of the larger data set to which reference is made. Similarly, in testing three factors for an association with lung cancer (passive smoking, cooking with kerosene, and burning incense), it would be useful to conduct an analysis that will allow evaluation of the effect of each after adjustment for the other two.

The suggestive evidence that passive smoking is more likely associated with adenocarcinoma in peripheral rather than central locations may be logical but is weak, especially considering the lack of analytical rigor. The ratio of ETS-exposed cases of adenocarcinoma to the total is 18 out of 32 (56%) for central locations and 19 out of 28 (68%) for peripheral locations. This difference is not statistically significant ($p = 0.26$ by Fisher's exact test). Consequently, the "apparent association" between passive smoking and peripheral adenocarcinoma (and not central tumors) may well be due to chance alone. There is suggestive evidence in the data that passive smoking may be associated with lung cancer ($OR = 2.01$, $p < 0.03$ for a one-sided test), but that is based only on the crude odds ratio in unmatched data and needs to be confirmed by a more thorough evaluation of the data that takes potential confounders into account. Overall, this study provides some suggestive evidence for an association between passive smoking and lung cancer. Potential confounders (including age) have not been controlled for, however, so attribution of the elevated odds ratio to ETS exposure is uncertain.

A.24. LEE

A.24.1. Author's Abstract

"In the latter part of a large hospital case-control study of the relationship of type of cigarette smoked to risk of various smoking-associated diseases, patients answered questions on the smoking habits of their first spouse and on the extent of passive smoke exposure at home, at work, during travel and during leisure. In an extension of this study an attempt was made to obtain smoking habit data directly from the spouses of all lifelong non-smoking lung cancer cases and of two lifelong non-smoking matched controls for each case. The attempt was made regardless of whether the patients had answered passive smoking questions in hospital or not.

Amongst lifelong non-smokers, passive smoking was not associated with any significant increase in risk of lung cancer, chronic bronchitis, ischemic heart disease or stroke in any analysis.

Limitations of past studies on passive smoking are discussed and the need for further research underlined. From all the available evidence, it appears that any effect of passive smoke on risk of any of the major diseases that have been associated with active smoking is at most small, and may not exist at all."

A.24.2. Study Description

This study was undertaken in England, essentially from 1979-83. Its stated objective is to investigate the relationship between passive smoking and risk of lung cancer in nonsmokers. It is an outgrowth, however, of a hospital-based case-control study to assess whether the risk of cardiorespiratory disease associated with smoking varies by type of cigarette smoked. It was initiated in 1977 in 10 hospital regions in England. In 1979, interviewers began gathering information on passive smoking as well in four of the regions. Then in 1982, this case-control study of the effects of passive smoking was begun using nonsmoking cases identified by the ongoing cardiorespiratory effects study. For the new study, spouses of cases and specially selected controls were interviewed regarding smoking habits. Previously collected data on passive smoke exposure obtained from patients back to 1979 were used.

Basically, two substudies were conducted. One used the data obtained directly from hospitalized cases and controls to address several sources of passive smoke, including spousal (henceforward the "passive smoking" study); the second substudy used data obtained from the *spouses* of cases and controls along with corresponding information from the patients themselves, when available, to address spousal smoke exposure only (henceforward the "spousal smoking" study). Cases for the passive smoking substudy were currently married lifelong nonsmokers diagnosed with lung cancer (of any cell type), chronic bronchitis, ischemic heart disease, or stroke in one of four participating hospital regions. Controls were currently married lifelong nonsmoker inpatients diagnosed with a condition definitely or probably not related to smoking and individually matched on sex, age, hospital region, and, when possible, hospital ward and time of interview. Thus, density sampling was used when possible. For the spousal smoking substudy, previously married patients were excluded; the same criteria otherwise applied, except that controls were now matched on sex, age decade, and—as far as possible—hospital and time of interview.

Diagnoses were obtained from medical records. Exposure data were obtained through apparently unblinded, presumably face-to-face interviews with inpatients and their spouses. A total of 3,832 married cases and controls were interviewed regarding passive smoking through 1982; it is unclear how many potential subjects refused or died before interview. Only 56 of these

were married lung cancer cases meeting the spousal smoking study criteria. Spousal interview data were obtained for 34 of these cases and 80 controls; interviews were refused by the remainder. Although matching of cases and controls was initially carried out, it was not retained in the analysis, and no demographic comparison of cases and controls used in the analyses is provided. Diagnoses were apparently drawn from patients' charts, provisional diagnoses were used where no final diagnosis was specified, no data on diagnostic technique(s) or histology is presented, and no diagnostic verification is reported.

The patient population consists of never-smokers, defined as lifelong nonsmokers, which presumably excludes cigar and pipe smokers. Exposure to ETS is approached in several ways. The primary exposure is that of a spouse smoking manufactured cigarettes at some point over the course of a marriage. Spousal smoking in the 12 months before interview was also assessed. In addition, "regular" exposure to passive smoke in various situations (i.e., at home or work, during travel or leisure) was assessed. The first two exposures were quantified in numbers of cigarettes smoked per day, the others in terms of "not at all, a little, average, or a lot." Thus, it appears that cigar and pipe smoking may not have been included in the spousal smoking exposures. Comparison of individual responses regarding spousal smoking status by patients and their spouses revealed a high degree of concordance (97%) for smoking during the last 12 months and a substantial concordance (85%) for smoking during marriage. No other checks on exposure data were reported.

The ETS patient data set includes 56 cases and 112 controls who met the initial study criteria. Not all of these answered each passive exposure question, however, and not all met the criteria for the spousal interview study. Similarly, spouses of 34 cases and 80 controls provided exposure information of varying completeness. Thus the numbers involved in each analysis varied considerably. For smoking during marriage, data obtained directly from spouses indicated that for males and females combined, 24 of 34 lung cancer cases and 51 of 80 controls were exposed, which yields a crude odds ratio of 1.4 for spousal smoking. With standardization for age, an odds ratio of 1.33 (95% C.I. = 0.50-3.48) was reported. Data obtained from qualifying patients, in contrast, revealed 13 of 29 cases and 27 of 59 controls to be exposed, yielding a crude *and* adjusted odds ratio of 1.00 (95% C.I. = 0.41-2.44). Stratification by gender yielded adjusted odds ratios from spousal interview data of 1.60 (0.44-5.78) and 1.01 (0.23-4.41) for females and males, respectively, with corresponding odds ratios from patient interview data of 0.75 (0.24-2.40) and 1.5 (0.37-6.34). When spouses identified as smokers by interview with either source were classified as exposed, an odds ratio of 1.00 (0.37-2.71) was obtained for female subjects. For the larger inpatient passive smoking study population, age-standardized odds ratios for passive smoke

exposure at home, at work, during travel, and during leisure revealed no consistent associations, with as many negative as positive relationships observed after adjustment for both age and whether still currently married. The same inconsistency held true for spousal smoking during the last 12 months and during the whole marriage. Adjustment for working in a dusty job reportedly did not affect the conclusion that passive smoking was not associated with risk.

Spousal smoking was slightly negatively associated with chronic bronchitis, ischemic heart disease, and stroke, whereas a combined ETS exposure index was negatively associated with heart disease but positively associated with bronchitis and stroke.

The author concluded that the findings appear consistent with the general view, based on all the available evidence, that any effect of passive smoking on risk of lung cancer or other smoking-associated diseases is at most quite small, if it exists at all. The marked increases in risk noted in some studies are more likely to be a result of bias in the study design than of a true effect of passive smoking.

A.24.3. Comments

The heart of this study is the spousal interview investigation of lung cancer and spousal smoking. Only 34 case spouses and 80 control spouses, and even fewer of the corresponding cases and controls themselves, are included, which gives the study low statistical power. Because the study began with hospital inpatient married lifelong nonsmokers, and matching on several key factors was employed, good comparability of cases and controls would seem readily achievable. No case-control demographics are provided, however, and matching is abandoned in the analyses. Undoubtedly, the high rate of refusals and frequency of omitted responses (themselves a potential source of selection and information bias) contributed to the decision to abandon matching, with the aim of preventing further substantial reduction in numbers through exclusion of unmatched subjects. The unfortunate result is that the comparability of the cases and controls is uncertain. At least all are drawn from the same four hospital areas within a fairly limited timespan, which, in combination with the other study criteria, reduces the likelihood of serious noncomparability.

Numerous opportunities for misclassification of disease and exposure status are present. Current working diagnoses are apparently drawn from patient charts without verification, and controls are selected from patients with diagnoses judged either probably or definitely not associated with smoking by unspecified criteria. This creates considerable potential for misclassification, both through inaccuracies in diagnoses generally and through inclusion of smoking-related diseases in the control group particularly, which would produce a downward bias in results. Exposure misreporting and recall problems would seem least likely where spouses are

interviewed directly about exposure within the last 12 months. Results for this situation are not presented, although they are reportedly similar to those for smoking during marriage.

The larger inpatient study elicited smoking data from patients, and only for their *first* spouse for patients who had remarried; thus, exposure occurring in subsequent marriages is not addressed. In addition, no information on duration or level of smoking in marriage is used in any of the spousal smoking analyses. The most likely result of these problems is nondifferential misclassification resulting in a bias toward the null. For general estimated home, work, travel, or leisure exposure to passive smoke, rough quantification *is* attempted by having patients categorize their exposure as "not at all, a little, average, or a lot." By necessity, this is a very subjective evaluation, and people more acclimated to smoke and tolerant of exposure might well tend to characterize a given amount of exposure as less severe than would a person of less tolerance who more actively avoids exposure. This tendency would produce a bias toward negative association.

Standardization for age and restriction of cases and controls to currently married lifelong nonsmokers should control potential confounding by age, marital status, or active smoking, although misreporting of current or former active smoking cannot be ruled out entirely. Dusty occupation reportedly had no effect on the larger inpatient study results. Potential confounding by race, socioeconomic status, diet, cooking habits, or any additional factors was not addressed.

One might expect the most accurate reporting of spousal smoke exposure when spouses are interviewed directly regarding their own smoking habits, and the most inadvertent misclassification when patients are queried about the smoking status of their first marital partner only. Analyses along these lines yielded slightly positive associations with smoking for the former and negative with the latter approach. No consistent pattern of association was seen for other sources and lung cancer, although high combined exposure scores were associated positively with chronic bronchitis and stroke and negatively with ischemic heart disease.

In summary, this study presents equivocal results that neither strongly confirm nor refute the hypothesis that passive smoking mildly increases risk of lung cancer. The quality of the study, however, is a limitation. The discrepant results for subject-supplied data (OR = 0.75) and spouse-supplied data (OR = 1.60), varying degrees of completeness of information on subjects, the subjective nature of questions regarding ETS exposure, and lack of information on intensity or duration of husband's smoking do little to inspire confidence in the study's data and, consequently, the results from analysis of those data.

A.25. LIU

A.25.1. Author's Abstract

"In Xuanwei County, Yunnan Province, lung cancer mortality rates are among the highest in China in both males and females. Previous studies have shown a strong association of lung cancer mortality with indoor air pollution from 'smoky' coal combustion. In the present case-control study, 110 newly-diagnosed lung cancer patients and 426 controls were matched with respect to age, sex, occupation (all subjects were farmers), and village of residence (which provided matching with respect to fuel use). This design allowed assessment of known and suspected lung cancer risk factors other than those mentioned above. Data from males and females were analyzed by conditional logistic regression. In females who do not smoke, the presence of lung cancer was statistically significantly associated with chronic bronchitis (odds ratio [OR] = 7.37, 95% confidence interval [CI]: 2.40-22.66) and family history of lung cancer (OR 4.18, 95% CI: 1.61-10.85). Females' results also suggested an association of lung cancer with duration of cooking food (OR 1.00, 9.18 and 14.70), but not with passive smoking (OR 0.77, 95% CI: 0.30-1.96). In males, lung cancer was significantly associated with chronic bronchitis (OR 7.32, 95% CI: 2.86-20.18), family history of lung cancer (OR 3.78, 95% CI: 1.70-8.42), and personal history of cooking food (OR 3.36, 95% CI: 1.27-8.88). In males a dose-response relationship of lung cancer with smoking index (years of smoking/amount of smoking) was shown by risks of 1.00, 2.61, 2.17 and 4.70."

A.25.2. Study Description

This study was undertaken in Xuanwei county of China's Yunnan Province, a county whose lung cancer mortality rates are among the country's highest and wherein burning of smoky coal indoors in unventilated pits is a common practice. The study sought to assess "the influence of factors other than type of fuel on the occurrence of lung cancer in Xuanwei."

Cases of newly diagnosed lung cancer occurring among farmers at hospitals and clinics in Xuanwei between November 1985 and December 1986 were identified as potential study subjects. Up to five controls were identified for each case, depending on availability after matching on age (± 2 years), gender, and village of residence. A total of 112 cases were identified, from which 2 were excluded due to unknown addresses. Of 452 candidate controls, 26 were excluded due to erroneous questionnaire responses. All subjects were interviewed face-to-face by trained personnel using a standardized questionnaire, and blinding extended to both interviewers and interviewees.

The final study groups consist of 54 (56) female (male) cases and 202 (224) female (male) controls. Mean age is 52 years for both cases and controls, who are also similar in family size, ethnicity, birthplace, dwelling type, and type of fuel used (smoky coal, wood). Separate breakdowns for males and females are not provided. Very few of the cases (19/110 = 17%) were histologically or cytologically diagnosed, and no verification of diagnosis or exclusion of secondary tumors was undertaken (except to monitor mortality among some of the cases).

Exposure to ETS was not evaluated for males. Among females, only one subject (a control) reported ever having smoked, so the ETS population of females effectively consists of never-smokers. Subjects were classified as exposed to ETS if their household contained at least one smoker. Exposure is not quantified, and it is unclear whether former or only current exposure is intended. No checks on exposure status or consideration of marital status are mentioned, and no histological data are presented.

The ratio of exposed to unexposed female subjects is 45 out of 94 (176/202) for cases (controls), yielding a crude odds ratio of 0.74. A conditional logistic regression analysis adjusted for other risk factors (presumably the other factors referred to are age-began-cooking and years-of-cooking) gives an odds ratio of 0.77 (95% C.I. = 0.30-1.96). No further analyses of ETS exposure are provided.

Four non-ETS factors are significantly associated with lung cancer among females: family history of lung cancer (OR = 4.18; 95% C.I. = 1.61-10.85), personal history of bronchitis (OR = 7.37; C.I. = 2.40-22.66), age-began-cooking (OR = 2.44-1.03, but with a reversing and nonsignificant dose-response), and years-of-cooking (OR = 2.49-2.25, nonsignificant trend). Among males, significant positive associations were noted for total smoking index, often-cooking-own-food, family history of lung cancer, and history of chronic bronchitis, whereas age-began-smoking, years of smoking, and intensity of smoking showed modest but nonsignificant associations with lung cancer.

The authors conclude that "it is quite conceivable that the large amount of air pollutants inhaled during indoor smoky coal burning in Xuanwei partly overwhelm the carcinogenic effect of tobacco smoking" and "may also overwhelm the carcinogenic effect of passive smoking." "Our results disclose important associations of lung cancer with factors other than fuel type and therefore indicate that those factors must be considered in any comprehensive, quantitative risk assessment of lung cancer in Xuanwei. Our results also confirm indirectly that smoky coal pollution is an important determinant of lung cancer in Xuanwei."

A.25.3. Comments

This modestly sized study was not designed to test for effects of ETS exposure. Rather, it is an hypothesis-generating exercise aimed at covering a broad range of possible risk factors. Within that context, the study has considerable merit, but as an investigation of ETS it has numerous flaws.

Restriction to farmers minimizes concerns with occupation and overall lifestyle, and control selection, including matching on age, gender, and village, produced demographically comparable case and control populations for males and females combined despite the enigmatic exclusion criterion for controls. It is unknown, however, whether the groups remain comparable after subdivision into males and females.

The use of newly diagnosed cases reduces potential selection bias due to inclusion of prevalent cases, but the heavy reliance (83%) on clinical and radiological diagnosis and the absence of independent confirmation or exclusion of secondary tumors introduces a strong potential for misclassification of disease and precludes analyses by cell type. The observation that follow-up of a number of lung cancer patients revealed that almost all died within 6 months of diagnosis does little to confirm diagnostic validity, contrary to the authors' interpretation. Such presumably random misclassification would make detection of an existing ETS-lung cancer association more difficult.

Exposure data collection procedures, particularly the exclusive use of face-to-face interviews without resort to proxies and the blinding of both interviewers and subjects, are laudable. For ETS, however, the exposure measure used is nonspecific and nonquantitative. Complications due to past exposure and differences in degree or duration could distort the observed disease-exposure relationship, probably biasing results toward no effect.

Potential confounding is not adequately addressed in the statistical analysis. The authors are particularly concerned with indoor smoky coal burning due to the known strong correlation between smoky coal use and lung cancer mortality in Xuanwei. Wishing to focus their investigations on factors other than smoky coal, they matched cases and controls on village, which "provided effective matching on fuel type." But because age and a host of other demographic factors, as well as smoky coal consumption, were comparably distributed in cases and controls (see Study Description), these factors were not considered further in the data analysis. This is a serious flaw, for pair matching was not retained in the analysis; thus, none of the above factors is effectively controlled for. The conditional regression analyses do control for risk factors other than those cited above, but exclusion of age, fuel type (e.g., smoky coal), and degree of exposure to fuel fumes may produce misleading results.

The presence of other significant risk factors for lung cancer makes detection of an effect from ETS, if present, less likely. Masking by the presence of smoky coal and other factors in the study environment is probably a factor in the remarkably weak association between active smoking and lung cancer among study males (adjusted OR = 1.36). If even an effect of active smoking remains largely obscured under study conditions, it is unlikely that an effect of ETS would be detected.

Overall, this study makes important contributions to its principal objectives but is not helpful in assessing ETS and lung cancer. It is observed, for example, that persons in areas of Xuanwei with high lung cancer rates (and high smoky coal consumption) may inhale more BAP (benzo-[a]-pyrene) by spending 8 hours indoors than by smoking 20 cigarettes. Due to such factors, the authors observe, "the effect of passive smoking on lung cancer may depend on local environmental factors and results obtained in a given region may therefore not be applicable to other regions." Avoidance of areas atypically rich in competing exposures and careful control of potential confounders and interactive risk factors must be key objectives in studies of ETS and lung cancer.

A.26. PERS

A.26.1. Author's Abstract

"The relation between passive smoking and lung cancer was examined by means of a case-control study in a cohort of 27,409 nonsmoking Swedish women identified from questionnaires mailed in 1961 and 1963. A total of 77 cases of primary carcinoma of the bronchus or lung were found in a follow-up of the cohort through 1980. A new questionnaire in 1984 provided information on smoking by study subjects and their spouses as well as on potential confounding factors. The study revealed a relative risk of 3.3, constituting a statistically significant increase ($p < 0.05$) for squamous cell and small cell carcinomas in women married to smokers and a positive dose-response relation. No consistent effect could be seen for other histologic types, indicating that passive smoking is related primarily to those forms of lung cancer which slow the highest relative risks in smokers."

A.26.2. Study Description

This case-control study, undertaken to explore the role of passive smoking in lung cancer, is based on cohorts of Swedish women assembled prior to 1963. Nonsmokers were drawn from these cohorts to create matched case and control groups.

Cases are nonsmoking Swedish women included in the Swedish National Census or Twin Registry who responded to smoking status questionnaires in 1961-63 and who subsequently developed primary lung or bronchial cancer by 1980. Two control groups were cumulatively sampled from National Census or Twin Registry subjects who did not develop lung or bronchial cancer. In group 1, two controls were matched to each case on year of birth ($\pm$ 1 year). In group 2, two controls were matched to each case (2:1) on year of birth ($\pm$ 1 year) and vital status in 1980. Thus, there were 58 cases and 232 controls from the National Census and 34 cases and 136 controls from the Twin Registry. A follow-up questionnaire that included questions on spousal and parental smoking habits was distributed to each subject or the next-of-kin in 1984. Out of 92 cases of tracheal, bronchial, lung, or pleural cancer occurring by 1980, 15 cases in which a diagnosis of primary cancer of the lung or bronchus was not established were excluded. Exclusion of women indicated to be active smokers according to the 1984 questionnaire, or for whom ETS exposure information was not available, eliminated a further 10 cases. Active smoking and lack of exposure information eliminated 21 of the 368 controls initially assembled. Histological confirmation was available for 64 of the 77 cases with primary lung or bronchial cancer; 12 cases were cytologically confirmed; and the remaining case was verified at autopsy.

Never-smokers are subjects who report that they have never smoked any form of tobacco. A woman is ETS-exposed if she has ever been married to a tobacco smoker; for women married more than once, only the longest marriage is considered. Exposure to spousal smoking is quantified in units of cigarettes per day or packs of pipe tobacco per week; parental smoke exposure is defined as 0, 1, 2, etc. (equal to the number of parents who smoke). No other sources of ETS exposure are considered. Never-smoking status was checked by comparing the responses to the 1961-63 questionnaires with those obtained in 1984. Data on sources of ETS were not checked. Never-married women were classified as nonexposed to spousal smoke; widows and divorcees were classified according to the smoking status of the former husband with whom they had lived the longest. Of the never-smoking cases for whom passive smoking information was available, squamous and small cell tumors constituted 20 cases, 13 of whom were exposed to spousal smoke; of the other 47 cases, 20 were exposed to spousal smoke.

Responses to the ETS questionnaire were available for a total of 81 never-smoking cases and 347 never-smoking controls. The 67 cases with primary lung or bronchial cancer constitute the ETS study subjects. It is not clear how many of the 347 potential controls were employed in each analysis. Presumably many (up to 4 for each excluded case from the original 81 never-smoking cases) were not used in the matched analysis, whereas most or all were used in the unmatched analyses described subsequently.

A total of 33 of the 67 cases were exposed to spousal smoking. Among the never-smoking women, matched analyses indicate that the odds ratio for marriage to a smoker is 3.8 (95% C.I. = 1.1-16.9) for squamous or small cell cancer compared to control group 1, 3.4 (0.8-20.1) compared to control group 2, and 3.3 (1.1-11.4) compared to both groups combined. For other cell types, corresponding odds ratios are 0.7, 0.8, and 0.8, respectively. Subsequent analyses abandoned matching and pooled all controls. For squamous and small cell cancer, high exposure to spousal smoking (15 or more cig./day or at least one pack of pipe tobacco/week for 30+ years) is associated with an age-adjusted odds ratio of 6.4 (1.1-34.7), whereas the lower exposure is associated with an odds ratio of 1.8 (0.6-5.3). The estimated odds ratios for other types of cancer are also elevated for the higher exposure, but not at the lower one. Odds ratios adjusted for age and spousal smoking when at least one parent smokes as well are above 1 (1.9; 95% C.I. = 0.5-6.2) for squamous and small cell types but not for other types.

Logistic regression analyses reportedly produced the same results as did the stratified analyses. In addition, occupation, household radon, and urban or rural status had no significant effect. It is notable, however, that for all cancers combined, the odds ratio for radon exposure is 1.4 (0.4-5.4), the odds ratio for spousal smoking is 1.2 (0.6-2.6), and the odds ratio for radon and spousal smoking combined is 2.5 (0.8-8.5). No separate analyses for squamous and small cell cancer are provided for radon and other potential confounders. The authors conclude that exposure to ETS is related primarily to the forms of lung cancer that show the highest relative risks in smokers. The results are internally consistent.

A.26.3. Comments

Although based on cohorts assembled for other purposes, this case-control study was specifically designed to investigate passive smoke exposure. Thus, all participants are ETS subjects, which are matched. Matching criteria are rather modest—birthdate (± 1 year) for control group 1 and birthdate and vital status for control group 2. Because the study targeted *all* cases detected in the same cohorts from which matching controls were randomly drawn, good comparability of cases and controls is likely. No demographic comparisons of cases and controls for whom ETS information was available—and thus who constituted the analytical subjects—were provided to confirm this, however. Data on active smoking among subjects were collected both at the start and after the end of mortality monitoring, providing an opportunity to verify the nonsmoking status over time and exclude individuals whose status had changed (apparently those reported in 1984 to have smoked daily for at least 2 years were so excluded). Thus, the probability of significant misclassification of active smoking status is low. Data on passive

smoking were collected only after the end of mortality monitoring and by necessity employed proxy respondents extensively, so some misclassification of exposure is likely. Self-administration of questionnaires eliminates interviewer bias as a source of error, making misclassification less likely to be systematic, but preferential recall of smoke exposure by relatives of cancer victims could have produced a bias. Misclassification of disease is unlikely to have been a problem because most cases were histologically diagnosed and secondary lung cancers were excluded.

Consideration of spousal smoke exposure only in their longest marriage among women married more than once means that some of the unexposed group probably had substantial exposure to spousal smoking, creating a bias toward no association. Classification of all never-married women as unexposed despite possible smoking by cohabitants creates the same bias. Few subjects (less than 20%) were single, but the frequency of remarriage is unknown; therefore, it is unclear how important this bias might have been. Lack of consideration of workplace smoke exposure may also have contributed a bias toward the null hypothesis of no association.

The authors addressed a number of potential confounders. Restriction of subjects to women eliminates potential confounding by gender, and age is addressed by retaining age-matching or, alternatively, adjusting for age in all analyses. Reportedly neither occupation, radon, nor urban residence had significant confounding effects, which makes confounding by other factors related to socioeconomic status or lifestyle unlikely, too. An analyses of parental smoking controlled for spousal smoking. The authors do, however, present evidence that the odds ratio for simultaneous exposure to radon and spousal smoke approximately equals the sum of the separate odds ratios for radon and spousal smoke, consistent with additivity of the effects. But, perhaps due to limited numbers, they report results only for all cancers combined rather than for the squamous and small cell subgroup in which the only *significant* spousal smoking association was observed.

In summary, this study reports a consistent, dose-related, and (for high exposure levels) statistically significant positive association between exposure to spousal tobacco smoke and squamous and small cell carcinoma of the lung; a positive but nonsignificant association was also observed for parental smoke exposure. No significant associations were observed for other cell types. The observed associations apparently are not due to confounding by other major risk factors, although dietary and smoking habits were not directly addressed. A possible recall bias cannot be ruled out but seems unlikely given the negative results obtained for cancers other than squamous and small cell. The study provides a useful contribution to investigation of the relationship between ETS exposure and lung cancer.

A.27. SHIM

A.27.1. Author's Abstract

"A case-control study of Japanese women in Nagoya was conducted to investigate the significance of passive smoking and other factors in relation to the etiology of female lung cancer. A total of 90 nonsmoking patients with primary lung cancer and their age- and hospital-matched female controls were asked to fill in a questionnaire in the hospital. Elevated relative risk (RR) of lung cancer was observed for passive smoking from mother (RR=4.0; $p<0.05$) and from husband's father (RR=3.2; $p<0.05$). No association was observed between the risk of lung cancer and smoking of husband or passive smoke exposure at work. Occupational exposure to iron or other metals also showed high risk (RR=4.8; $p<0.05$). No appreciable differences in food intakes were observed between cases and controls."

A.27.2. Study Description

This study was undertaken in Nagoya, Japan, during 1982-85 to investigate the significance of passive smoking and other factors such as occupational history, domestic heating system, and dietary habits in the etiology of lung cancer in nonsmoking Japanese women. All data were collected specifically for this study, which was limited to never-smokers.

All subjects were obtained from four hospitals in Nagoya. Cases are women with primary lung cancer (of any type) treated in these hospitals between August 1982 and July 1985 who reported themselves to be never-smokers and consented to interview. Controls are women with a diagnosis other than lung cancer from the same or adjacent wards with controls matched 2:1 with cases on age ($\pm$ 1 year), hospital, and date of admission. Cases were not restricted to incident disease, but controls were essentially density-sampled by admission date. Data collection was by self-administered questionnaire; no attempt at blinding is described. Of 118 female lung cancer cases treated during the study period, four refused to participate in the study and 24 were excluded as current or former smokers. Only a single matching control could be found for 17 of the cases. No other information on loss of potential controls is provided. There is a total of 90 (163) cases (controls), with 52 (91) currently married to a smoker. Cases and controls share identical age ranges (35-81 years) and have nearly identical mean ages (59 years for cases, 58 for controls). All cases were histologically diagnosed, excluding secondary lung cancers.

All study subjects are self-reported never-smokers. A number of individual sources of ETS in the home are considered, including smoking by mother, father, husband, father-in-law, mother-in-law, offspring, and siblings. For each of these sources, smoking in the home at any time constituted exposure. Workplace exposure was characterized simply as presence or absence;

for other exposures, the number of cigarettes per day was obtained. In addition, data on length of marriage, time spent in the same room as the wife, and total number of cigarettes smoked were obtained for husbands. Exposure data were not checked, and marital status was not considered in the design or analysis of the study. The predominant type of lung cancer is adenocarcinoma (69 out of 90 cases), followed by squamous (13), large cell (4), small cell (3), and adenoid cystic carcinoma (1). No data on airway proximity are provided.

Logistic regression was used to estimate the relative risk for each source of ETS exposure. No significant association with lung cancer was noted for smoking by the husband (RR = 1.1), father (RR = 1.1), husband's mother (RR = 0.8), offspring (RR = 0.8), or siblings (RR = 0.8); smoking by the subject's mother (RR = 4.0) and by the husband's father (RR = 3.2), however, are significant ($p < 0.05$). None of eight dietary factors, including green-yellow vegetable and fruit intake, demonstrated a significant association, nor did type of cooking fuel or frequency of cooking oil use. Occupational history of exposure to iron or other metals shows a moderately strong but nonsignificant association (RR = 2.8), whereas for use of kerosene, coal, or charcoal heating there is a mild association (RR = 1.6-1.7).

Simultaneous stratification by father-in-law's and mother's smoking indicates that the effects of the two exposures are not additive. Smoking by father-in-law, smoking by mother, and occupational metal exposure were included simultaneously in a logistic regression model. After adjusting the effect of each variable for the other two, the relative risk for maternal smoking, father-in-law's smoking, and metal exposure are 2.1, 3.2 ($p < 0.05$), and 2.4, respectively. The authors conclude that the exposure to tobacco smoke from household members (i.e., mother or husband's father) could be associated with female lung cancer. As the precise situation of passive smoking in the home or other places is still unclear, however, they find that further studies are needed to clarify the significance of passive smoking in relation to the etiology of lung cancer in Japanese women.

A.27.3. Comments

This study employs a moderate number of well-matched cases and controls. Their comparability appears good, as supported by the identical age ranges and similar mean age and occupational categories for the two groups. A further strength of the study is its lack of reliance on proxy information with attendant potential for inaccurate recall. Exposure information was obtained from self-administered questionnaires, which eliminates the possibility of interviewer bias but may lead to inaccuracy due to misinterpretation of questions or varying care in their completion. Such problems with exposure information would tend to mask any actual association.

Lung cancer was histologically diagnosed in all subjects and secondary lung cancers excluded, so diagnostic accuracy appears good for cases. Control diagnoses, however, were not validated, so some smoking-related disorders (in addition to the heart conditions noted in 3% of controls) may be included among the controls, a problem that once again would tend to reduce any observed association.

Restriction of subjects to never-smokers maximizes efficiency because effects of passive smoking would likely be dwarfed by active smoking. But it is unclear precisely what subjects were asked about their smoking status. Were any cut-points regarding pack-years or cigarettes per day specified? Was former smoking specifically questioned? Thus, some misclassification of smoking status may have occurred, and if a greater proportion of persons with smoking family members misreport themselves to be never-smokers, this would create an upward bias.

The authors restrict their assessment of exposure from relatives to at-home smoking, which may be more meaningful than total smoking as a potential source of passive smoke exposure. Furthermore, they collected data on smoking habits of all relatives, not just spouses or parents, thus reducing the chance of missing an exposure source. On the other hand, there is no consideration of total household smoking (all sources combined), cumulative exposure (except for husbands), or of pipe or cigar smoking; nor is there differentiation of current and former exposure--all potential sources of exposure misclassification, which would tend to make an association more difficult to detect.

Of the several sources of ETS exposure at home, only the relative risks for smoking by the mother and by the father-in-law are suggestive, and both of these are significant ($p < 0.05$). When these sources are considered simultaneously, however, and the effect of each is adjusted for the other, smoking by the husband's father remains significant ($RR = 3.2$; $p < 0.05$) but the effect of mother's smoking is diminished ($RR = 2.1$) and is not statistically significant. The authors' emphasis on the significance of exposure in childhood from maternal smoking appears misplaced. Exposure from the father-in-law is, of course, in adulthood. There is no evidence of an effect from husband's smoking ($RR = 1.1$), however, and these exposure sources were considered simultaneously so that the effect of one could be adjusted for the other. The large number of comparisons (e.g., eight groupings of passive smoke exposure, alternative spousal exposure measures, and several occupational and eight dietary factors) increases the likelihood that an observed relative risk will appear to be significant by chance alone (the effect of multiple comparisons).

Another aspect of the statistical analysis worth noting is that, although cases and controls appear well matched on age, hospital, and hospital admission date, these factors and other

potential confounders are not included in an adjusted analyses of the data (aside from the example with three sources of exposure described above). Consequently, possible confounding cannot be ruled out, although the demographic similarities between cases and controls make severe confounding less likely.

In summary, this study presents some interesting results. It finds a strong (adjusted RR = 3.2) and statistically significant association between father-in-law's smoking at home and lung cancer and associations for maternal smoking and occupational metal exposure as well. The lack of association for any of the other sources of ETS examined could be due to problems with exposure assessment and control disease criteria. Equally, however, given the unclear treatment of matching factors in the analysis, and the number of variables explored, the few substantial associations noted might be due to chance, confounding, or both. Were potential confounders clearly treated in their analyses, this study would have made a stronger contribution. As it stands, the study's data are of moderate utility, providing the number of comparisons and limitations regarding bias are kept in mind.

A.28. SOBU

A.28.1. Author's Abstract

"A hospital-based case-control study among non-smoking women was conducted to clarify risk factors in non-smoking females in Japan. Cases consisted of 144 non-smoking female lung cancer patients, and these were compared to 713 non-smoking female controls. The odds ratios (95% confidence interval) for use of wood or straw as cooking fuels when subjects were 30 years old was estimated as 1.77 (1.08 to 2.91). For those whose household members, other than husbands, had smoked, the odds ratio was estimated as 1.50 (1.01 to 2.32). For those whose mothers had smoked, the odds ratio was estimated as 1.28 (0.71 to 2.31). Use of heating appliances did not show an elevated risk. Some points to be noted in this study of low-risk agents for lung cancer are discussed."

A.28.2. Study Description

This study was conducted in Osaka, Japan, to clarify risk factors for lung cancer in nonsmoking females in Japan. Of interest are the roles of both active and passive smoking and other indoor air pollutants, particularly smoke or fumes from sources of indoor cooking and heating. This article reports only on female nonsmokers in the study, which is not matched on any variables. A very similar article presenting interim results and using slightly fewer subjects than the one described here is by Sobue and coworkers (1990).

Cases consist of all newly admitted lung cancer patients in eight Osaka hospitals between January 1986 and December 1988. Controls were collected from newly admitted patients in one or two other wards of the same hospitals during that period. Almost 90% of the controls were admitted as cancer patients, about half of which were diagnosed with breast cancer. Self-administered questionnaires designed for this study were completed by both cases and controls at the time of hospital admission. Cases are incident and control sampling is density, unmatched aside from the time of hospital admission (within 1.5 years). The entire study, including active smokers and males, consists of 295 (1,079) female (male) cases and 1,073 (1,369) female (male) controls. Nonsmoking females compose 156 cases, of which there was missing information on 12. The resultant number of ETS subjects is 144 (731) female nonsmoking cases (controls). The age distribution of the cases (controls) is as follows: 40 to 49, 20 (238); 50 to 59, 34 (229); 60 to 69, 41 (186); and 70 to 79, 34 (78). The corresponding percentages are 14 (33), 34 (31), 28 (25), and 24 (11), which indicates that controls tend to be younger than cases. Also, the mean age of cases (controls) is 60 (56). There was no systematic review of histological diagnosis. All original diagnoses were confirmed microscopically, however, and all the pathologists involved in the eight participating hospitals were experienced specialists in lung cancer. Thus, the likelihood of secondary lung cancers among the cases should be small.

Several sources of ETS exposure are included, all of which occur in the home. Exposure in adulthood is expressed by two measures--smoking by the husband and by other household members (the last category consists chiefly of households where the husband's father and/or sons smoke). Three sources of exposure in childhood are considered--father smokes, mother smokes, and other household members smoke. No information is provided on how exposure to spousal smoking is handled for unmarried women (single, divorced, or separated). The entire complement of cases and controls is included in the summary data for each of the five sources of exposure given above. If only married women were included in the study, no mention of it was found.

The histological data for ETS subjects are not classified by exposure to ETS, but the percentage of cases by cell type are given: squamous cell (8), small cell (5), adenocarcinoma (78), large cell (5), and other (4). The ETS data on spousal smoking consists of 80 out of 144 (exposed/total) cases and 395 out of 731 controls, for an odds ratio of 1.13 (95% C.I. = 0.78-1.63). (Our calculations give 1.06 [0.74-1.52].) The odds ratio for ETS exposure from other household members in adulthood is 1.57 (95% C.I. = 1.07-2.31). (Our calculated values are 1.77 [1.21-2.58].) For ETS exposure in childhood by the father, by the mother, and by other household members, the respective odds ratios are 0.79 (95% C.I. = 0.52-1.21), 1.33 (95% C.I. = 0.74-2.37), and 1.18 (95% C.I. = 0.76-1.84). Tests were conducted by the Mantel-Haenszel procedure, with

stratification by age and education (two levels). Analysis by logistic regression, adjusted for age at time of hospitalization, was conducted for two of the exposure measures described above with similar outcomes. Based on this evidence, the author concludes that for childhood exposure, a slight increase of risk was suggested for those with smoking mothers, although statistical significance was not observed. For exposure in adulthood, an elevated risk was estimated for those with smoking household members other than husbands.

The statistical analysis includes exposure to sources other than ETS, namely, the use of wood or straw as cooking fuel, the use of heating equipment that pollutes the room with combustion products, and the use of charcoal foot warmers. All exposures considered, including ETS, are smoke or fumes from products burned indoors. It is concluded that significantly elevated risks were observed for subjects who had used wood or straw as cooking fuels at 30 years of age (OR = 1.89; 95% C.I. = 1.16-3.06). No elevated risks were found for sources of indoor heating (use of kerosene, gas, coal, charcoal, and wood stoves without chimneys). Similarly, no significance was found for the use of charcoal foot warmers, a practice that was popular until the 1960's.

A.28.3. Comments

With 144 cases and 731 controls, the sample size is larger than many of the other case-control studies on ETS. Information on cases and controls was obtained by self-administered questionnaire, which is generally considered less reliable than face-to-face interviews. The questionnaires were presumably completed by the subjects themselves in all cases, however, which is preferable to proxy-supplied information. The information supplied was not verified from other sources, as noted by the authors in reference to testing for biomarkers of exposure to tobacco smoke (they note that laboratory tests can only detect recent exposure, but they could still be useful in eliminating current smokers who may misreport themselves as never-smokers). Although cases and controls were newly diagnosed patients within a short time period in the eight participating hospitals and were supplied with the same questionnaire, there are still some questions regarding the comparability of cases and controls and their representativeness of the target population.

Controls tend to be younger than cases: Mean ages are 56 and 60, respectively, and 33% of controls, compared to 14% of cases, are below the age of 40. Controls also tend to be more educated than cases, with 69% of controls having completed 10 or more years of education compared to 52% of cases. Differences in age and educational level further reflect differences in lifestyle and socioeconomic status that may affect risk of disease. Also, the controls are

predominantly cancer patients too, almost half with breast cancer. Although the diseases of the controls may not be known to be related to tobacco use, controls may be a biased sample (as noted by the authors). Furthermore, the statistical analysis stratifies on age and education so, even though cases and controls were not strictly matched on these variables, the reported results should not be due to confounding by either of these factors. On the other hand, exclusion of breast cancer controls reportedly leaves the results unchanged.

Although some of the issues and reservations described above are methodological in nature and apply to the study throughout, others are specific to the ETS data alone. For example, one might expect a question regarding the use of cooking with wood or straw at age 15 and at age 30 to be open to little subjective interpretation or error in recall, presuming that methods of cooking persisted for several years between changes within a household. Although there is some suggestive evidence of increased lung cancer from ETS exposure (the reservations above set aside for the moment), the statistical evidence may be stronger for an association between lung cancer prevalence and use of wood or straw for cooking at age 30. Further support is provided by the observation that among those who had used wood or straw for cooking at age 30, 90% had also used those fuels at age 15, suggesting extended exposure in most cases. The age distribution of those exposed to wood or straw cooking is not given, but exposure at 30 years of age and before would allow for the long latency expected for lung cancer because 86% of the patients are at least 50 years of age.

The smoke from cooking sources may obscure or distort any impact of ETS exposure because the two sources probably contain some of the same carcinogens. The temporal dimension of exposure may also be a factor because indoor smoke from cooking may be less common at present than 30 years ago in comparison to ETS exposure. Further statistical analysis to adjust the effect of ETS exposure for the presence of smoke from cooking might aid interpretation of the results in this study, depending on the extent of confounding present.

A.29. STOC

A.29.1. Author's Abstract

(*Note:* This study has not been published. Only the abstract is available, which is given below.)

"Risk factors for lung cancer among women who had never smoked cigarettes were examined in an ongoing, population based, case-control study conducted in Florida. One hundred and twenty-four primary carcinomas of the lung, and 241 control women who had never smoked were included. Results suggest that childhood and adult exposures to environmental tobacco smoke may increase the risk of lung cancer among women who never smoked cigarettes. Having a

husband who smoked cigarettes resulted in a statistically significant increase in risk of lung cancer among women who had never smoked, with an odds ratio of 1.8 (95% C.I. 1.1-2.9). A 40% increase in risk was observed among women with less than 25 years of exposure to a spouse who smoked, when compared to women who reported their spouse had never smoked, with the risk increasing to 60% among women exposed 25 years or longer.

When exposure to tobacco smoke in childhood was considered, the data were less consistent. Having a parent who had smoked during the respondent's childhood did not increase the risk of lung cancer. However, among those respondents with high levels of exposure to parental smoking, an excess risk, although not statistically significant, was observed. Never smoking women who accumulated 25 or more exposure years experience a 70% increase in risk (OR = 1.7, 95% C.I. 0.8-3.6) of lung cancer compared to women who reported neither parent had smoked cigarettes."

A.30. SVEN

A.30.1. Author's Abstract

"In a population based-case control study the association between female lung cancer and some possible etiological agents was investigated: 210 incident cases in Stockholm County, Sweden, and 209 age-matched population controls were interviewed about their exposure experiences according to a structured questionnaire. A strong association between smoking habits and lung cancer risk was found for all histological subgroups. Relative cancer risk was found for all histologic subgroups. Relative risk for those who had smoked daily during at least one year ranged between 3.1 for adenocarcinoma to 33.7 for small cell carcinoma in a comparison with never-smokers. All histological types showed strong dose-response relationships for average daily cigarette consumption, duration of smoking, and cumulative smoking. There was no consistent effect of parental smoking on the lung cancer risk in smokers. Only 38 cases had never been regular smokers and the risk estimates for exposure to environmental tobacco smoke were inconclusive. The high relative risks of small cell and squamous cell carcinoma associated with smoking may have relative implications for risk assessments regarding passive smoking."

A.30.2. Study Description

This study was undertaken in Stockholm County, Sweden, from 1983 to 1986 to investigate the association between female lung cancer and some possible etiologic agents, particularly active and passive smoking. Because active smoking was an exposure of interest, cases and controls were not matched on smoking status; thus, the ETS study population is unmatched.

Cases are Swedish-speaking women with primary lung cancer from three Stockholm County hospitals who were willing and able to be interviewed between September 1983 and December 1985. Cases with carcinoid tumors were excluded from the ETS analysis. Both population and hospital-based control groups were assembled. Population controls were women randomly selected from the county population register, matched to a case on birthdate and interviewed between September 1983 and December 1986. Hospital controls were subjects originally interviewed as potential lung cancer cases but subsequently diagnosed with nonmalignant conditions. Population controls were enlisted and interviewed as soon as a case's diagnosis was confirmed, but because this confirmation took as long as a year after the interview, controls were not density sampled. Unblinded interviews were conducted face to face with all cases (and hospital controls) and 58% of the total population controls; the remainder were interviewed by telephone.

After exclusion of 21 potential cases due to initial diagnostic uncertainty, refusal, or illness precluding interview, 210 confirmed cases remained. Elimination of 172 ever-smokers and four subjects with carcinoid or not-microscopically-confirmed tumors left 34 never-smoking cases. Similarly, 209 population and 191 hospital controls were included in the total study, but a combined total of only 174 were never-smokers. The total case population averaged 62.5 years of age, but no other demographic information regarding cases or controls is provided. All cases used in the ETS analyses were histologically or cytologically confirmed primary lung cancers.

Daily smoking for at least 1 year is the criterion for a smoker; all other persons are considered never-smokers. Pipe and cigar smoking are never specifically addressed. Exposure to ETS is calculated for four sources: mother, father, home, and work. Having a smoking mother or father (at any time during ages 0-9 years) constitutes exposure to that particular source, whereas the presence of a smoker at home and work constitutes exposure. Adulthood and total lifetime exposure are considered separately for home and workplace exposure. Exposure levels are arbitrarily scored 1 for nonexposure, 2 for exposure to one source, and 3 for exposure to both sources in trend analyses of never-smokers, where exposures are considered in pairs (i.e., maternal and paternal smoking, home and workplace exposure). No other units of ETS exposure are used. Adenocarcinomas constituted 22, squamous cell 5, and small cell 2 of the 34 lung cancers occurring among never-smokers in the ETS population; no further histologic details regarding the ETS study population are provided.

To maximize available case numbers, parental smoking was first analyzed among all cases and community controls using stratification to adjust for active smoking (cig./day) and age. A risk of 1.8 (95% C.I. = 0.5-7.0) was estimated for maternal smoking and 0.8 (0.3-1.4) for paternal

smoking. A trend analysis in which maternal, paternal only, and no parental smoke exposure were scored as 3, 2, and 1, respectively, revealed no indication of trend ($p = 0.9$). Analyses restricted to never-smokers used both community *and* hospital-based controls combined. Among cases (controls), for childhood up through 9 years of age, 3 (5) had smoking mothers, 12 (71) had smoking fathers (but not mothers), and 19 (98) were unexposed. This yielded an age-adjusted risk estimate of 3.3 for maternal smoking (with or without paternal smoking) and 0.9 for paternal smoking during childhood. Adult exposure at home *and* at work yielded an estimated risk of 2.1, whereas exposure at home *or* work yielded a risk of 1.2. For lifetime exposure, the estimated risks for exposure as both a child *and* adult and as either a child *or* an adult were 1.9 and 1.4, respectively. None of these associations were statistically significant, and no significant trends were observed. The authors conclude that the results pertaining to ETS in the present study were not conclusive. The small number of never-smokers among the cases could be one important reason. It should be noted, however, that most of the point estimates of relative risk were greater than unity, which agree with results from previous studies on ETS exposure and with risk estimates concerning active smoking.

A.30.3. Comments

This study was undertaken to explore the role of active as well as passive smoking in lung cancer. After exclusion of active smokers, the available number of cases is too small to yield much statistical power.

Cases and population-based controls were initially matched on date of birth, but this matching was abandoned in the ETS analysis; furthermore, unmatched hospital-based controls are combined with the population-based controls in most analyses to boost available numbers. The comparability of these groups is thus unclear, and the authors provide no demographic comparisons to facilitate assessment of this potential problem. The reported similarity of results using only population-based controls is reassuring, but no details are provided as to *how* similar results actually were.

Diagnostic misclassification of cases is unlikely, given the histological or cytological confirmation of all cases and exclusion of secondary cancers. All cases were interviewed face to face, but 42% of controls were interviewed by telephone. The accuracy of responses may thus be lower for controls than for cases. And because interviews were not conducted blindly, inflation of estimated associations through interview bias is possible. A potential bias is also introduced by the rather large amount of active smoking required for classification as an ever-smoker. This allows considerable active smoking among persons in the never-smoker group, the effect of which could

mask an effect of passive exposure, or, if covarying positively with passive smoking, cause overestimation of association.

The first set of analyses of paternal and maternal smoking includes ever-smokers while attempting to adjust for active smoking on the basis of average daily cigarette consumption. The adequacy of this adjustment is questionable given the large estimated risks associated with active smoking relative to those posited for passive smoking, so the elevated estimated risks for maternal smoking obtained in these analyses are of questionable validity.

Restriction of the analyses to never-smokers similarly produces an elevated odds ratio for maternal smoking of 3.3, but the numbers involved (three cases and five controls) are so small that this value is quite unstable. A pattern of increasing estimated risk with increasing sources of exposure (at home or at work) as an adult and increasing periods of exposure (in childhood or adulthood) over the lifetime is suggestive of an association between lung cancer and ETS, but again small numbers preclude statistical significance of these results.

Restriction of the study population to females rules out the possibility of confounding due to gender. The likelihood of an ethnicity effect is reduced by restriction to Swedish-speaking residents of Stockholm County, and age is reportedly controlled for in all analyses. No other potential confounders are addressed. For example, marital status is not considered in the analyses of spousal smoking, leaving open the possibility that nonsmoking-related differences between married and unmarried women contributed to the observed association. The reported similarity of results when only population controls were used instead of hospital and population controls combined provides a general argument against confounding, although no specifics regarding the degree of similarity were supplied.

In summary, this study presents consistent evidence of associations between lung cancer and maternal, home, and workplace passive smoking exposure. Limited numbers preclude statistical significance and interviewer bias or confounding due to dietary or other factors cannot be ruled out as contributors to the observed results. Bearing these limitations in mind, the study's results are inconclusive but (excluding the analyses that include active smokers) do make a useful contribution to the pool of information available regarding ETS and lung cancer.

A.31. TRIC

A.31.1. Author's Abstract

"Fifty-one women with lung cancer and 163 other hospital patients were interviewed regarding the smoking habits of themselves and their husbands. Forty of the lung cancer cases and 149 of the other patients were nonsmokers. Among the nonsmoking women there was a

statistically significant difference between the cancer cases and the other patients with respect to their husbands' smoking habits. Estimates of the relative risk of lung cancer associated with having a husband who smokes were 2.4 for a smoker of less than one pack and 3.4 for women whose husbands smoked more than one pack of cigarettes per day. The limitations of the data are examined; it is evident that further investigation of this issue is warranted."

A.31.2. Study Description

This study was undertaken in Athens, Greece, to investigate the relationship of spousal smoking and lung cancer. All female Caucasian Athenian residents admitted to one of three chest or cancer hospitals in Athens and assigned a final diagnosis of lung cancer other than adenocarcinoma and alveolar carcinoma from September 1978 through June 1980 were interviewed by a physician. Controls were gathered from nonsmoking female Caucasian Athenian patients hospitalized during the same time period in the Athens Orthopedic Hospital. Some prevalent cases were thus presumably included, so control sampling probably approximated a density approach but did not strictly conform to one.

Diagnostic information was obtained from patients' charts. Exposure information was obtained by face-to-face unblinded interviews conducted by the same physician for all subjects. A total of 51 cases and 163 controls were interviewed. Of these, 11 cases and 14 controls reported themselves to be active smokers, leaving 40 cases and 149 controls as ETS subjects. No interview refusals are reported. Mean age of cases (controls) is 62.8 (62.3) years. Husband's education was marginally higher in controls than cases with 63% and 58% of spouses having completed primary school, respectively. No other demographic comparisons are reported for the ETS subjects alone. For the sample population including smokers, factors such as age, duration of marriage, occupation, education, and urban versus rural residence are all similar for cases and controls, except once again educational level is slightly higher for controls. There is no indication that verification of diagnosis or exclusion of secondary lung cancers was undertaken in cases. Of the 51 total cases, 14 were diagnosed histologically, 19 cytologically, and 18 by radiological or clinical means. No breakdown is given for the ETS subjects alone.

The study classifies as nonsmokers both reported never-smokers *and* former smokers who quit more than 20 years ago. It is not mentioned whether cigar and pipe smoking are considered as sources of exposure. Nonsmoking women are considered exposed to ETS if they are married to a man classified as a smoker. The average number of cigarettes smoked per day by the husband and the number of years of marriage are used to estimate the total number of cigarettes smoked by the husband during marriage. No data on childhood or nonspousal ETS exposure were collected.

Single women are grouped with women married to a nonsmoker and are thus considered unexposed. Widowed or divorced women were classified according to their former husband's smoking status on the assumption that smoking stopped at death or divorce. No checks of exposure information are reported.

For ETS subjects, the number of cases (controls) exposed over the total is 29 to 40 (78/149). The crude odds ratio calculated by the reviewers is 2.4 (95% C.I. = 1.12-5.16). The results presented in the article are all stratified by level of husband's smoking. The odds ratios are 1.8, 2.4, and 3.4 when the husband is a former smoker, smokes 1 to 20 cigarettes per day, and smokes 20 or more cigarettes per day, respectively. No confidence intervals are given, but a test for upward trend was statistically significant ($p < 0.02$). When ETS exposure is estimated by total number of cigarettes smoked during marriage, odds ratios (1.3, 2.5, and 3.0) increase with cumulative exposure (1-99, 100-299, and 300+ thousand, respectively). The upward trend remains statistically significant at $p < 0.02$. No analyses adjusted for age or other potentially confounding variables. With regard to age and other demographic variables, the authors conclude from the similarity of cases and controls that it is not necessary to stratify for these variables in the analysis, particularly because none is significantly associated with smoking in the study.

The authors note that this study has obvious limitations and is offered principally to suggest that further investigation of this issue should be pressed. Most seriously, the numbers of cases are small. Nevertheless, the association is in the direction expected if passive smoking is related to lung cancer, and the outcome is unlikely to be due to chance. Other limitations noted include the high percentage (35%) of cases lacking cytology and the selection of controls from a hospital different from those of the cases; it is argued, however, that neither of these appears to be consequential. The observation is made that it is potentially easier to detect an effect of passive smoking in the Greek population than in most Western populations, because in the latter groups, the overwhelming effects of active smoking, together with the high correlation between smoking habits of spouses, would tend to confound and conceal the lesser effects of passive smoking.

A.31.3. Addendum

In a letter to the editor of *Lancet* in 1983, Trichopoulos et al. released a data table derived from extension of subject collection through December 1982. This nearly doubled the sample size used in the 1981 publication, yielding 77 nonsmoking cases (102 total) and 225 smoking controls (251 total). The crude odds ratio calculated by the reviewers is 2.08 (95% C.I. = 1.20-3.59). The results for the expanded study show very little change; (estimated) relative risks when husbands

are former smokers, (1-20 cig./day and > 20 cig./day) compared to nonsmokers are 1.95, 1.95, and 2.54, respectively. The test for upward trend in the dose-response is significant (p = 0.01). No other analyses are presented.

A.31.4. Comments

This study was conceived and undertaken to explore the association of spousal smoking with lung cancer and does not rely on a preexisting data set. Thus, the investigators were in a position to design their selection and data collection to maximize the strength of their findings. This did not, however, prevent the appearance of some design and analytical flaws.

Demographics of the total case and control populations are very similar. All subjects in the spousal smoking analysis are resident Athenian nonsmoking women hospitalized in the same area of Athens; case and control groups have very similar mean ages, and their husbands are comparable in education. Thus, the groups probably have good demographic comparability, although it would have been helpful if the detailed demographic comparisons were focused on the nonsmokers alone. Most of the controls (108 out of 163) were being treated for fractures, a relatively minor and nonchronic illness compared to lung cancer, which may make them more representative of the general community than of hospitalized patients as a whole. This should reduce the problem of inclusion of smoking-related illnesses in the control group.

Although the researchers sought to exclude adenocarcinomas and alveolar carcinomas, presumably considering these would be less smoking-related, nearly two-thirds of the cases were not histologically confirmed, so an indeterminate number of these cell types was probably included. More important, the infrequency of histologic confirmation and lack of mechanisms to verify diagnoses or primary tumor status introduces potential for misclassification. The likely effect is a bias toward no association.

The researchers clearly devoted considerable thought to the smoking and exposure criteria, particularly with regard to changes in smoking and marital status over time. Single women were, however, automatically classified as unexposed. The authors contend that this is warranted by the traditional nature of Greek society and report that analyses restricted to married women result in similar, and still statistically significant, associations, although with somewhat lower estimated risks. There is a small reduction in the odds ratios after exclusion of single women, however, and the restriction of the full analyses and results to married women may have been useful.

Another issue related to exposure concerns inclusion of former smokers in the study, provided they had not smoked for at least 20 years. Active smoking 20 to 30 years before the onset of lung cancer may be of etiological relevance, however, in view of a long latency period for

lung cancer. Although use of the same interviewing physician for all subjects eliminates the problem of interobserver variability, it magnifies the potential problem of interviewer bias in exposure assessment, presumably toward a positive association, because the interviews were apparently conducted unblinded (virtually unavoidable with regard to diagnosis, given that controls were drawn from orthopedic trauma and rheumatology wards).

A larger concern, however, is the issue of potential confounders. It is contended that the similar distribution of demographic variables between cases and controls eliminates the need to consider these variables in the analyses, but similarity between cases and controls does not preclude confounding from an independent risk factor differentially distributed by *exposure*. More convincing is the contention that these variables were not significantly associated with smoking in these data, although no specifics are included. Potential confounders such as diet, cooking, and heating practices are not addressed. The appearance of a statistically significant trend, for ETS exposure measured by either current spousal smoking or cumulative cigarette consumption during marriage, supports an association between spousal smoking and increased lung cancer incidence.

Overall, the issues addressed above would probably produce a conservative bias, resulting in an underestimate of the degree of association. The study's basic design is sound. It provides statistically significant evidence of dose-response, and although the limitations described above should be borne in mind, it provides useful data for assessment of the relationship between ETS and lung cancer.

A.32. WU

A.32.1. Author's Abstract

"A case-control study among white women in Los Angeles County was conducted to investigate the role of smoking and other factors in the etiology of lung cancer in women. A total of 149 patients with adenocarcinoma (ADC) and 71 patients with squamous cell carcinoma (SCC) of the lung and their age- and sex-matched controls were interviewed. Personal cigarette smoking accounted for almost all of SCC and about half of ADC in this study population. Among nonsmokers, slightly elevated relative risk(s) (RR) for ADC were observed for passive smoke exposure from spouse(s) [RR = 1.2; 95% confidence interval (CI) = 0.5, 3.3] and at work (RR = 1.3; 95% CI = 0.5, 3.3). Childhood pneumonia (RR = 2.7; 95% CI = 1.1, 6.7) and childhood exposure to coal burning (RR = 2.3; 95% CI = 1.0, 5.5) were additional risk factors for ADC. For both ADC and SCC, increased risks were associated with decreased intake of β-carotene foods but not for total preformed vitamin A foods and vitamin supplements."

A.32.2. Study Description

This study was undertaken in California during 1981 and 1982 to investigate the role of smoking and other factors in the etiology of lung cancer in women. These other factors included prior lung disease, coal heating and cooking, diet, and occupation. Both active and passive smokers are included; some of the ETS analyses retain active smokers while attempting to adjust for smoking status.

Cases are white female English-speaking Los Angeles County residents under 76 years of age at time of diagnosis with primary adenocarcinoma or squamous cell cancer of the lung between April 1, 1981, and August 31, 1982. Cases are restricted to U.S.-, Canadian-, or European-born individuals with no history of prior cancer other than nonmelanoma skin cancer. Controls are density sampled, matched individually on neighborhood and age ($\pm$ 5 years), and meet all case criteria (except, of course, diagnosis of lung cancer). The L.A. County tumor registry was used to identify incident cases for inclusion in the study, whereas controls were recruited house to house. Interviews to obtain exposure data were conducted by telephone with participating subjects, apparently unblinded.

A total of 490 eligible cases were identified; 270 were not interviewed because they were too ill or had died (190), their physician refused permission to contact them (28), they could not be located (8), or they refused (44). Those not interviewed did not differ significantly from those interviewed with regard to age or their marital, religious, or smoking status as recorded on registry records. Refusals eliminated 70 potential controls. The case and control populations had nearly identical mean ages for adenocarcinoma, 59.7 versus 59.5 years, respectively, and for squamous cell cancer, 61.4 versus 61.1 years. No other demographics are provided. Histologic diagnoses were obtained for all cases.

For spousal smoking, exposure constitutes having a spouse who smoked while living with the subject. For workplace smoke, exposure is based on the opinion of the subject. It is not clear whether for the lung cancer analyses, parental smoking refers only to adult life (as for spousal and workplace exposure) or to the childhood and teen years (as was stipulated for coal and preadult lung disease exposures). Adult life seems most probable. Units of exposure for spousal and parental smoking are cigarettes per day and years of exposure, apparently entered into a regression model as a combined variable; for occupational exposure, units are in years of exposure. Exposure data were apparently not checked, treatment of cigar and pipe smoking is never mentioned, and no results are reported for household smoking aside from spouse and parents, although information on this exposure was collected. Never-married women were excluded from the spousal smoking analysis, but marital status was not otherwise considered in the analyses. The

only histologic or airway proximity information provided for the ETS subjects is that 29 adenocarcinomas occurred among nonsmokers, 12 of which were bronchoalveolar.

The total study population includes 220 cases and an equal number of matched controls. Of the cases, 149 are adenocarcinoma and 71 are squamous cell. Nonsmokers constituted 29 of the adenocarcinoma cases and 62 of the corresponding controls, while composing 2 of the squamous cell cases and 30 of the controls. No raw data are presented regarding passive smoking and lung cancer. Logistic regression analysis of matched pairs was used in all calculations. Results restricted to nonsmokers are presented only for adenocarcinoma. An estimated relative risk of 1.2 is found for spousal smoking, 1.3 for workplace exposure, and 0.6 for smoking by either parent. None of these estimates was statistically significant. Exposure from spouses and at work, however, show a dose-response trend with years of exposure, yielding estimated relative risks of 1., 1.2, and 2.0, for 0, 1 to 30, and 30 or more years of exposure, respectively.

Analyses that include active smokers but attempt to adjust for them by including the number of cigarettes smoked per day and age at start of smoking in a logistic regression model are presented for both lung cancer types. For adenocarcinoma, estimated relative risks for maternal, paternal, spousal, and workplace exposure of 1.7, 1.3, 1.2, and 1.2, respectively, were obtained. For squamous cell cancer, maternal, paternal, spousal, and workplace relative risks are 0.2, 0.9, 1.0, and 2.3, respectively. None of these estimates is statistically significant.

History of lung disease at least 5 years prior to diagnosis of lung cancer reportedly had no significant association with lung cancer. History of lung diseases before age 16 yielded a significant association for pneumonia (RR = 2.7 [95% C.I. = 1.1-6.7] for adenocarcinoma and RR = 2.9 [95% C.I. = 0.5-17.4] for squamous cell cancer) but not for six other diseases.

Heating or cooking with coal during the childhood and teenage years is also significantly associated with lung cancer (RR = 2.3 [95% C.I. = 1.0-5.5)] for adenocarcinoma and RR = 1.9 [95% C.I. = 0.5, 6.5] for squamous cell). Among dietary factors, low beta carotene consumption is significantly associated with adenocarcinoma (RR = 2.7) and mildly associated with squamous cell (RR = 1.5). Diets low in dairy products and eggs have similar relative risk values. No significant associations were noted for vitamin A consumption, occupation, or other health history factors not previously considered.

The authors conclude that the etiology of squamous cell carcinoma can be explained almost entirely by cigarette smoking. Cigarette smoking, however, explains only about half of the adenocarcinoma cases. On the basis of this study, childhood lung disease and exposure to coal fires in childhood explain at least another 22% of adenocarcinoma cases. Passive smoking and

vitamin A may be involved, but more research is needed to clarify their roles in lung cancer etiology.

A.32.3. Comments

This study took particular care with its treatment of case and control assembly. Extensive inclusion criteria extending to both groups, matching not only on age but neighborhood of residence, and retention of matching through analysis all bode well for comparability of cases and controls. The virtually identical mean ages of cases and controls indicate the success of these efforts. In addition, exclusive use of incident cases reduces the potential for selection bias, and density sampling of controls reduces potential problems with temporal variation. The only real fault in the treatment of cases and controls is the failure to provide any demographic comparison other than for age, thus denying concrete confirmation of high case-control comparability.

Case diagnoses are likely to be accurate, because all were histologically diagnosed, making misclassification unlikely and making cell-type-specific analyses possible. Although no one pathologist or team verified these determinations, the authors note that there is generally good interobserver agreement for the cell types included in this study. Potentially eligible cases not interviewed due to illness, refusal, or other reasons did not differ significantly in demographic or smoking status from those actually interviewed, again arguing against biased selection.

No proxy interviews were used and all subjects were English-speakers, enhancing the chances of obtaining accurate exposure information. On the other hand, interviews were by telephone—possibly decreasing accuracy relative to face-to-face interviewing--and apparently unblinded, thus introducing possible interviewer bias toward positive results.

Collection of exposure data seems generally adequate, except that treatment of pipe and cigar smokers is not described. Uncertainty on this point extends to the analysis and is coupled with a vague treatment of parental smoking (current only? childhood only? or both?) and lack of treatment of household smokers other than parents or spouses, despite collection of data on this point. These uncertainties probably translate into nondifferential exposure misclassification, biasing results toward the null.

The analyses themselves suffer from the common problem of restricted numbers of nonsmoking cases—29 for adenocarcinoma and only 2 for squamous cell. Some factors examined are restricted to nonsmokers alone for adenocarcinoma, but for most analyses, an adjustment for active smoking by logistic regression modeling was attempted. The adequacy of such adjustment may be questionable. For adenocarcinoma, however, the results for passive smoking were very similar, regardless of whether restriction or adjustment was used. Further, a dose-response

pattern was seen for cumulative years of spousal and workplace exposure among nonsmokers. The utility of the smoking-adjusted cell analyses is nevertheless questionable, given the paucity of nonsmoking cases.

The findings of substantial associations between lung cancer (or, at least, adenocarcinoma) and childhood pneumonia and coal burning are of interest. It must be borne in mind that seven adult respiratory diseases (including pneumonia) as well as six other childhood respiratory diseases were examined, so the possibility that the pneumonia association was an artifact of multiple comparisons cannot be ruled out. History of hysterectomy and multiparity showed nearly significant associations with adenocarcinoma, but it is not clear how many other health history factors were also considered. Coal burning has been associated with lung cancer in several other studies. Similarly, as in several other studies, one found an association with low beta carotene intake, but there was no evidence of a dose-response gradient, and no significant association was found for preformed vitamin A. The strongest association with a dietary factor was actually that for low intake of dairy products and eggs, which showed a consistent dose-response pattern. The use of a matched-pair analytical approach controls for possible confounding due to age or neighborhood, which also reduces the likelihood of neighborhood-related factors such as socioeconomic status as major sources of bias. Confounding due to active smoking can be ruled out in the passive smoking results for adenocarcinoma and is not likely in regard to other factors given adjustment for this variable in all analyses. Likewise, the authors report that adjustment for childhood pneumonia, coal burning, and beta carotene intake did not alter their results. Strangely, however, no adjustment for dairy product and egg intake--the dietary factor with the most convincing association with lung cancer in their data--was carried out.

Overall, this study's results are consistent with a mild association between spousal and workplace ETS exposures and lung adenocarcinoma, although they support no such association for parental smoking. In addition, the study it raises childhood pneumonia, coal burning during early life, low intakes of beta carotene, and low intake of dairy products and eggs as potential moderate risk factors that should be considered by future studies. The results for squamous cell carcinoma are uncertain given the small number of nonsmoking cases available, and in all instances, they lack statistical significance due to sample size limitations. Thus, the study provides useful information on the relationship of adenocarcinoma of the lung with ETS and a number of other factors: information regarding squamous cell cancer is of much lower utility.

A.33. WUWI

A.33.1. Author's Abstract

"A case-control study of lung cancer involving interviews with 965 female patients and 959 controls in Shenyang and Harbin, two industrial cities which have among the highest rates of lung cancer in China, revealed that cigarette smoking is the main causal factor and accounted for about 35% of the tumors among women. Although the amount smoked was low (the cases averaged eight cigarettes per day), the percentage of smokers among women over age 50 in these cities was nearly double the national average. Air pollution from coal burning stoves was implicated, as risks of lung cancer increased in proportion to years of exposure to Kang and other heating devices indigenous to the region. In addition, the number of meals cooked by deep frying and the frequency of smokiness during cooking were associated with risk of lung cancer. More cases than controls reported workplace exposures to coal dust and to smoke from burning fuel. Elevated risks were observed for smelter workers and decreased risks for textile workers. Prior chronic bronchitis/emphysema, pneumonia, and recent tuberculosis contributed significantly to lung cancer risk, as did a history of tuberculosis and lung cancer in family members. Higher intake of carotene-rich vegetables was not protective against lung cancer in this population. The findings were qualitatively similar across the major cell types of lung cancer, except that the associations with smoking and previous lung diseases were stronger for squamous/oat cell cancers than for adenocarcinoma of the lung."

A.33.2. Study Description

The objective of this study was to evaluate the role of potential risk factors for lung cancer in Harbin and Shenyang, two cities among those with the highest mortality rate for lung cancer in China. Active smokers are included in the cases, so data on ETS subjects constitute a subset of the whole study.

Cases consist of female residents under age 70 newly diagnosed with primary lung cancer in about 70 participating hospitals in Harbin and Shenyang between 1985 and 1987. Controls are female residents randomly selected from the general population of these cities and frequency matched by 5-year age group to the age distribution of female lung cancer cases reported in the cities in 1983. Trained interviewers collected information on smoking habits, diet, cooking and heating practices, and other factors from subjects in face-to-face unblinded interviews.

A total of 1,049 qualifying cases were found, including both ever-smokers and never-smokers, of which 405 were diagnosed by histology, 309 by cytology, and 351 by radiology or clinical means. (Note: These diagnostic numbers do not total 1,049. The 351 figure may be

intended to be 251, which would give a total of 965 diagnoses, about the number of cases interviewed.) Of these, 85 either died prior to interview, refused to participate, or could not be located. Mean age of participating cases was 55.9 years, whereas that of the 959 controls was 55.4 years. Nonsmokers compose 417 of the interviewed cases and 602 of the controls.

A smoker is defined as a person who has smoked cigarettes for 6 months or longer, so a nonsmoker apparently may have smoked up to 6 months. Information on all types of tobacco products smoked was collected. Sources of ETS exposure include smoking by any household cohabitant and smoking by individuals (spouse, mother, and father) over the course of the subject's lifetime. Exposure at the workplace is also addressed. ETS exposure in the home is expressed in terms of cigarettes per day and number of years smoked; no units of measurement are used for workplace smoking. No checks on exposure data were undertaken. Marital status of subjects is not discussed. Of the cases with histological or cytological data, adenocarcinomas compose 310 (41.7%), squamous cell cancers 201 (28.9%), small and oat cell cancers 117 (16.8%), and large cell or unspecified types 66 (9.5%). No data on airway proximity or diagnostic breakdowns limited to nonsmokers are provided.

Statistical analyses of potential risk factors, including ETS, largely include data on active smokers and then adjust for the effect due to smoking by logistic regression, along with other potential confounders such as age, education, and location. These analyses indicate no increase in risk from household sources of ETS, with estimated relative risks of 0.8 (household cohabitants), 0.9 (spouse), 1.0 (mother), and 1.0 (father). The estimated risk for workplace exposure is nonsignificant (RR = 1.2). Restriction of analyses to ETS subjects alone (i.e., only the nonsmokers) produced similar results, with estimated relative risks of 0.7 for general cohabitant, 0.7 for spouse, 0.9 for mother, 1.1 for father, and 1.1 for workplace exposure. The ETS exposure from spousal smoking is significantly low (i.e., associated with a *decrease* in lung cancer by this analysis, as apparent from the confidence interval; RR = 0.7; 95% C.I. = 0.6-0.9).

The smoking-adjusted analyses indicate associations with lung cancer for several types of heating devices, including kangs (brick beds heated by pipes from the stove or by burners directly underneath), coal stoves, and heated brick walls or floors. The risk associated with the use of burning kangs (those heated by stoves underneath) shows an upward trend with years of use, becoming statistically significant at 21 or more years of use (RR = 1.5; 95% C.I. = 1.1-2.0). Significantly elevated risks are also associated with use of heated brick walls or floors (RR = 1.5 [1.1-2.1] for 1-20 years of use; RR = 1.4 [1.1-1.9] for > 20 years). Nonsignificant increases in risk are noted for use of kangs of all types, coal stoves, and coal burners; nonsignificant reductions in risk are indicated for noncoal stoves and central heat. Use of deep frying at least twice a month

and eye irritation during cooking are both significantly associated with lung cancer, as are regular intake of animal protein and fresh fruit. (Note: Multiple comparisons may be a factor for the apparent significance of some items, as discussed further in the next section.)

The authors find no overall association between lung cancer and ETS exposure. On the other hand, coal burning, exposure to cooking oil fumes, and chronic lung disease may all be risk factors. Consumption of beta carotene shows no evidence of a protective effect. Overall, active smoking is the major cause of lung cancer among women in the regions sampled.

A.33.3. Comments

The sample size is impressive, with ETS exposure data available for nearly 1,000 cases including smokers and over 400 cases when restricted to nonsmokers, thus providing substantial statistical power. All subjects are women recruited from two industrial cities in northeast China, reducing potential for complications due to regional or urban-rural differences. Nearly all of the hospitals in these cities were involved, all cases occurring in these hospitals were targeted, and the rate of participation among eligible cases was high; thus potential for selection bias is minimized. The effective case recruitment in combination with the use of general population controls maximizes generalizability of the study's results for northeast China. It would have been useful, however, to present the results for the two component study locations separately. Although coordinated in planning and execution, there are two separate study locations and the sources of heterogeneity between them tends to be obscured when results are combined.

Unfortunately, the study's results with regard to ETS are more limited than the strengths listed above might suggest. The inclusion of age, education, and location as control variables in all analyses is laudable, thus eliminating three sources of potential confounding. The attempt to control for potential sources of confounding that may be causally related to lung cancer by statistical methods, however, is less certain. Although some analysis was conducted with data for active smokers included, to the authors' credit they also analyzed data for ETS subjects alone (i.e., with the data for active smokers removed), which is the surest way to control for confounding by active smoking. Other potential causes of lung cancer (e.g., air pollution from coal-burning stoves, smokiness during cooking, and deep-fat frying foods) also need to be taken into account in an analysis of ETS. This cannot always be accomplished effectively by statistical methods, particularly when there are multiple risk factors to be taken into account that are variable, poorly measured, and possibly more potent risk factors than ETS may be.

At the risk of belaboring this point, as the reader is aware, a case-control study is ideally designed and executed under conditions where cases and controls are as comparable as possible

aside from the factor of interest, such as ETS exposure. The presence of other risk factors may tend to pollute and obscure, much like the contamination of a laboratory experiment. In this same sense, the presence of indoor sources of smoke other than ETS may contaminate an environment for measuring ETS effects because the non-ETS smoke likely contains many of the same carcinogens as ETS, and possibly in much larger quantities, depending on the relative levels of exposure. Other factors outside the home, such as workplace exposure to coal dust and to smoke from burning fuel that was reported more often in cases than controls, contribute to the potential confounding in a similar way. Consequently, a credible analysis of ETS requires being able to adjust for these likely confounding factors satisfactorily, and the ability to do that depends on reliable measures of exposure and the extent of confounding. That kind of statistical analysis is not given in the article, and it does not appear to have been possible, based on conversations with the authors (Wu-Williams and Blot) and the text of the article: "Despite the large size of our study, we were unable to clarify the magnitude of risks due to passive smoking, recognized as a cause of lung cancer around the world (U.S. DHHS, 1986). Perhaps in this study population the effects of environmental tobacco smoke was obscured by the rather heavy exposures to pollutants from coal-burning Kang, other indoor heating sources, and high levels of neighborhood air pollution (Xu et al., 1989)."

The multivariate analysis reported in the article reinforces the viewpoint that any ETS effect may be dominated by the presence of other risk factors. In that analysis, variables were allowed to enter a logistic regression model in the order of their explanatory value (a stepwise regression exercise in statistical terminology). The order of entry into the model is deep frying, eye irritation, pneumonia, household tuberculosis, burning kang, self-reported occupational exposure to burning fuel, passive smoking, and heated brick wall or floor. Passive smoking, in this exercise, is significant ($p < 0.05$) but in the direction of reducing lung cancer, not contributing to it. The 0.05 value, however is not fully meaningful as a significance level for ETS, because of the stepwise procedure used (the same data used in the construction of a model is used for testing variables in the model) and because of the likely confounding between ETS and other variables. Note, for example, that passive smoking entered the model ahead of heated brick wall or floor, which is highly significant when analyzed alone, whereas passive smoking is not.

The evidence for association of lung cancer with burning coal and deep frying foods is particularly provocative, as it indicates two factors that may play a substantial role in the etiology of lung cancer in northeast China and, hence, in other areas as well where such practices occur. The associations noted with other factors are also of interest, but their importance is undermined by the problem of multiple comparisons. In the table presenting results for dietary factors, for

example, 26 risk estimates are computed, 4 of which are significant at the 5% significance level (for a two-sided test, 2.5% level for the test of an effect), only one more significant finding than expected due to chance alone.

Being somewhat speculative, the use of cases age 70 and below may be a factor. Wells (1988) showed that about half of the female passive smoking deaths occur after age 70, for the studies included in that reference. If ETS is a risk for lung cancer and if individual susceptibility to lung cancer is a factor, some of the stronger risk factors such as coal burning and cooking oil may have caused lung cancer in the more susceptible subjects before passive smoking had a chance to exert itself.

In summary, this large and basically well-executed study observed no significant association between exposure to ETS from cohabitants, spouse, parents, or workplace and lung cancer. Lack of control for a number of other significant risk factors identified in the study undermines these results, however. The associations with coal burning for heat and oil frying are particularly notable. Use of the heating devices most strongly linked with lung cancer is presumably more common in colder northern regions, whereas stir frying may be more widespread in Asian communities, without regard to climate. Thus, this study was exploratory, designed to generate hypotheses rather than to test the specific hypothesis that ETS exposure is associated with lung cancer. It identifies a number of potential risk factors for consideration in future studies. The prevalence of these factors in the study population combined with the lack of analysis of their association with ETS exposure, however, renders the results for ETS inconclusive.

APPENDIX B. METHOD FOR CORRECTING RELATIVE RISK FOR SMOKER MISCLASSIFICATION

B.1. INTRODUCTION

The purpose of this Appendix is to present the details of the method used in Section 5.2.2. to correct observed passive smoking relative risks for the systematic upward bias caused by misclassification of some smokers as never smokers. The method used is that proposed by A. J. Wells and W. F. Stewart (Wells, 1990). This Appendix covers: Section B.2) the principles of the method; Section B.3) how the method differs from those previously used by the National Research Council and P. N. Lee; Section B.4) the data used to calculate the misclassification factors and other parameters; Section B.5) the mathematical model used to calculate the corrected relative risks; and Section B.6) a numerical example to show how the method is applied in a practical case. Evidence is also presented indicating that the true downward corrections for smoker misclassification bias may be even smaller than those used in Section 5.2.2.

There is considerable literature on this topic and a history of controversy regarding the magnitude of the bias and whether it may explain the observed increase in lung cancer mortality due to ETS exposure. The NRC report on the health effects of passive smoking (NRC, 1986) delves into this topic in considerable detail. It concludes that bias is likely and estimates an adjustment for the summary relative risk from the combined results for all ETS studies. The NRC report further concludes that smoker misclassification does not account for the observed passive smoking risk. On the other hand, Lee in various publications (Lee, 1987b, 1988, 1990, 1991) has claimed that the smoker misclassification bias is large enough to explain most or all of the observed passive smoking lung cancer risk.

Approaches to estimation of misclassification bias have used mathematical modeling with parameters estimated from a variety of sources that have not always been consistent. The procedure described below attempts to rectify some previous sources of misunderstanding on this topic and utilizes the extensive data sources now available to improve parameter estimates and tailor refinements to individual populations.

B.2. PRINCIPLES OF THE WELLS-STEWART METHOD

The Wells-Stewart method is based on the following principles, the nature and need for which have largely become apparent from the chronological evolution and disparate approaches and results on this problem.

Parameters:

a. Limit the misclassifieds to those who said they never smoked, not simply to nonusers, because the latter would include self-reported former smokers, who are not a factor in the epidemiology.

b. Use one minus sensitivity or its close relative, false negatives (misclassified smokers) divided by observed positives (self-reported smokers) as the vehicle for transferring misclassification data from cotinine and discordant answer studies to the passive smoking studies. Sensitivity is the term used to describe the fraction correctly classified as exposed, namely true positives divided by true positives plus false negatives, but since we are assuming that the true positives and the observed positives are the same (no misclassification of never-smokers as smokers). Sensitivity in this case becomes observed positives divided by observed positives plus false negatives. Thence one minus sensitivity becomes false negatives divided by observed positives plus false negatives. Ignoring the false negatives in the denominator introduces negligible error. In any case do not use specificity (true negatives divided by true negatives plus false positives) or any parameter that uses as its denominator true or observed negatives (self-reported never-smokers). The reason is that sensitivity is affected much less by smoker prevalence than parameters based on observed negatives.

c. Calculate a correction for each epidemiologic study separately using a misclassified smoker relative risk and a proportion of smokers among subjects and spouses that is characteristic of the timeframe and locale of each study. Use data from the study itself or from another study with the same target population, if possible.

d. Use only female data to correct misclassification of female subjects.

Mathematical model:

Calculate the corrected risk directly--that is, do not first calculate a bias assuming no passive risk and then divide the observed risk by that bias to get a corrected risk.

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Subjects found to be misclassified as nonsmokers are categorized according to their true smoking status--former or current. Current smokers are further classified as "regular" or "occasional", according to cotinine levels observed. "Regular" means the cotinine level is above 30% of the self-reported smoker mean; "occasional" applies to the range 10-30%. Cotinine levels are not informative for misclassified former smokers, who tend to be long term abstainers (10+ years, according to Lee (1987b) and Wald et al. (1986)). The two studies with detailed cotinine levels on female current smokers (Lee, 1986 and Haddow et al., 1986, in Table B-1) indicate that about 10% of the current smokers are occasionals.

B.3. DIFFERENCES FROM EARLIER WORK

The Wells-Stewart method differs from the method used by the NRC (1986), which is also described by Wald et al. (1986), in that the NRC method failed to separate the misclassified smokers into regular, occasional, and exsmokers, and they failed to account for the effect of smoker misclassification on active smoker risk. The NRC made an overall correction to the aggregated passive relative risk using United Kingdom smoking prevalence and risk rather than making the corrections study by study with appropriate smoking prevalences and risk for each study's time and locale, and they mixed male data with female data in arriving at misclassification factors. Their calculated bias of $1.34/1.25 = 1.07$, or 7%, for the combined worldwide studies is substantially higher than the 2% overall bias that would result if the biases in Table 5-7 were aggregated. The discrepancy is largely due to NRC's use of U.K. parameters for all of the studies regardless of locale, plus some overestimation of the impact of misclassified occasional and exsmokers.

Lee's methods have evolved over the years in three stages. In Lee (1987b, 1988) he improved on the NRC method in that he divided the misclassified smokers into exsmokers and current, regular and occasional smokers, and he corrected the smoker risk for misclassification. However, all of the five principles listed above were violated to some degree resulting in about a twelve-fold overestimation of the bias. The Lee (1990) paper correctly limits misclassifieds to never smokers, relates misclassified smokers to smokers, not to never smokers, and treats each study separately, but still mixes male input data with female data for use in calculating bias for females. Furthermore, his (Lee, 1990) mathematical model still relies on the assumption of no passive risk, which results in increased estimates of the bias as the observed relative risk increases. In addition, Lee (1990) has changed from separating the misclassified smokers into three groups in favor of the (less useful)

overall category of ever smokers. Most recently Lee (1991) presents a more complex mathematical model that includes a term for passive risk, but the method still has the other shortcomings noted for Lee (1990). A comparison of the most recent Lee bias estimates with those in Table 5-7 is shown in Table B-2 for the five U.S. studies with the greatest statistical weight. When Lee's inputs are used with the Wells-Stewart mathematical model, the calculated biases are if anything somewhat larger than when using Lee's most recent model. Therefore, the difference between Lee's most recent estimates of bias and those shown in Table 5-7 are in practical terms due almost entirely to differences in input parameters. The input parameters we have chosen are developed in the next section, and comparison with the Lee parameter estimates are shown as footnotes to Table B-2.

B.4. PARAMETER ESTIMATES

The key input into these calculations is the proportion of misclassified regular current smokers who claim they have never smoked. Our definition of misclassified regular current smokers, first suggested by Lee (1987b), produces a mean cotinine level approximately equal to that of all self-reported current smokers. Detailed data from three large cotinine studies have been assembled for use herein with the cooperation of their principal investigators (Coultas, Cumming, and Pierce in Table B-3). The data identify individual nonsmokers with cotinine values greater than 10% of the mean for self-reported smokers, by sex and self-reported smoking status (never or former). Data on nonusers are also available from several other studies (the lower portion of Table B-3). Since the numbers of misclassified smokers are small, the proportions of misclassified smokers who would have said "never" versus "former" are estimated using the proportions observed in the first three studies. Data sets not differentiating outcomes by sex have not been used. Also the large 1986 study by Haddow and colleagues has not been used for this purpose on the advice of one of the authors (private communication from G.J. Knight).

The number of self-reported never- and former smokers with sufficiently high cotinine levels to be reclassified as current smokers is shown by study in Table B-3. As described above, those with cotinine levels in the 10-30% range are considered to be occasional smokers while those above 30% are treated as regular smokers. If it is assumed that 90% of 1,525 self-reported current smokers, or 1,372, are regular smokers, leaving 10%, or 153, as occasionals, then the percentage of current regular smokers misclassified as never-smokers totalled over all studies in Table B-3 is 14/1,372 or 1.02%. The percentage is almost the same if the number of true, i.e., self-reported plus misclassified current

regular, smokers is used. For the occasional smokers only, the misclassification rate is much higher, about 20% (15%) of observed (true) occasional smokers. It is possible, however, that the subjects classified as occasional smokers based on cotinine levels in the range 10-30% may contain some true never-smokers that are just highly exposed to passive smoke.

The studies in Table B-4 provide data on discordant answers, i.e., reported never-smokers who have called themselves smokers on one or more previous occasions. Based on those data, the estimated percentage of former smokers misclassified as never-smokers is about 12% (11%) of the observed (true) number of former smokers. As mentioned previously, evidence suggests (Wald et al., 1986; Lee 1987b) that most former smokers misclassified as never-smokers have been nonsmokers for an extended period, such as 10+ years, and may have been light smokers on average. Accordingly, we have used a weighted average of the data of Alderson et al. (1985), Lubin et al. (1984), and Garfinkel and Stellman (1988) for 10+ year abstainers to estimate former smoker relative risk, namely, an excess risk that is 9% of current smoker excess risk.

Some confusion and misleading conclusions on smoker misclassification have resulted from the practice of expressing the number of smokers misclassified as never-smokers as a percentage of the total number of (either true or observed) never-smokers, rather than as a percentage of the number of smokers. That leads to a higher expected percentage of smokers misclassified as never- smokers among cases than controls because lung cancer cases are much more likely to have been smokers than never-smokers. Some people have interpreted a higher percentage of observed never-smokers later found to be misclassified smokers among the cases as evidence that smokers with lung cancer are more apt to claim falsely to be never-smokers than persons without cancer. That conclusion, however, appears to be an artefact of treating the misclassification rate as a percentage of the number of never-smokers rather than as a percentage of the number of smokers. The study data summarized in Table B-5 do not support that conclusion. If anything, it is more supportive of the conclusion that ever-smokers in lung cancer studies may be less likely to misrepresent themselves as never-smokers than members of the general public who are questioned in community surveys. The one percent average misclassification rate shown in Table B-5 for the lung cancer cases suggests that estimates such as the 5.7% from the general population studies (Table B-5) or the near four percent of ever-smokers (Table B-4) that we have used may be much too high.

Further corroboration that the misclassification rates from the community studies are too high relative to those in the epidemiologic studies is found in the recent study by Fontham et al. (1991).

After eliminating possible smokers among the self-reported never-smokers by the usual epidemiologic techniques, the investigators found by cotinine measurements that only two probable occasional smokers and no probable regular smokers were left among the 239 never-smoking lung cancer cases for which cotinine measurements were made. Assuming 45% ever-smoking among controls and an ever-smoker relative risk of 8 for regular smokers and 2.4 for occasionals, there would have been 1,456 smoker cases, consisting of 1,409 current smokers and 47 occasional smokers. It is seen that a misclassification rate of 0/1,409 = 0.00% for regular smokers is well below the 1.0% that we have used from the community surveys, and 2/47 = 4.3% for occasionals is also well below the 19.6% for occasionals that we have used.

Another indication that the estimates based on community surveys may be too high comes from analysis of male data. The observed percentage of never-smokers is typically much lower for males (17% to 35%) than females (41% to 86%). To correct for smoker misclassification we set up a deletions table analogous to Table B-15 where the number of current and former smokers misclassified as never-smokers are subtracted from the reported number of never-smokers. When the misclassification rates generated from community surveys are applied to the male data, the outcome is not credible--the number deleted for misclassification exceeds the total number of reported never-smokers in three of the eleven examples of which we are aware and drives the corrected relative risk well below unity in four more. This outcome indicates that the misclassification rates derived from the community surveys are too high. It is probable that the true smoker misclassification bias is on the order of one-fourth to one-half of the values shown in Table 5-7.

It is also said that East Asian women misclassify themselves at much higher rates than Western women. The data from the International Agency for Research on Cancer in Table B-3 do not support that claim, however, because the East Asia (Hong Kong, Japan, and China) misclassification rate for current regular smokers is 1/77 = 1.3%, not much different from the overall rate of 1.0%.

The main proponent of the idea that smoker misclassification accounts for most or all of the observed passive smoking risk has been P.N. Lee (1986, 1987b, 1988). He has estimated the bias for females to be as high as 1.24. However, his methods are open to considerable question. He used "nonuser" cotinine data, which includes people who said or would have said they were former smokers, rather than using only data on people who said they never smoked. This would about double the calculated bias. He averaged high male misclassification rates into low female misclassification rates. He made an overall correction to the combined risk using modern U.K. smoker risk and

smoking prevalence rather than making the corrections study by study, as is done here with smoker risks and prevalence appropriate for each study. He transferred misclassification rates from the cotinine and discordant answer studies using percent of never-smokers rather than percent of smokers. He also used as an input the data from the large Haddow study (Haddow et al., 1987) when the authors state (private communication from Dr. George Knight) that the data from the study should not be used for misclassification studies. Also Lee's mathematical method tends to overstate the bias for passive risks greater than about 1.3. At a risk of two, his method overstates the bias about 100%.

In conclusion, it would appear that the bias introduced by misclassification of smokers as never-smokers is not a serious problem. It probably increases perceived relative risks on a worldwide basis by 1% to 2%, with the effect being about three times as large for combined U.S. studies.

B.5. MATHEMATICAL MODEL

The proportion of observed smokers, m_{h0}, misclassified as never-smokers is estimated separately for former smokers (m_{10}), occasional smokers (m_{20}), and regular smokers (m_{30}). Similarly, the proportion of observed current smokers, m_{h1}, misclassified as former smokers is estimated separately for occasional smokers (m_{21}) and regular smokers (m_{31}). These estimates are given in Tables B-3 and B-4. It is assumed that there is no misclassification of true never-smokers as current or former smokers or of observed former smokers as current smokers. Also these misclassification factors are used for all the studies unless otherwise noted. We suspect that misclassification rates probably vary from study to study. That variability, however, would tend to cancel out as the individual study results are combined.

Let c_{ijk} designate the observed proportionate distribution of controls (i = 0) and cases (i = 1) by their smoking status (j = 0,1,2,3) and the smoking status of their husbands (k = 0,1) as illustrated in Table B-6. Following the notational convention that a dot in the subscript position means summation on that subscript, then $c_{0..} = c_{1..} = 1$.

The observed c_{ijk}'s are corrected for misclassification of the wife's smoking status by first specifying a 4 x 4 matrix of proportionate distribution (Table B-7), where P_{hj} (h,j = 0,1,2,3) is the probability that a subject with true smoking status h will also be observed to have smoking status j. The subscripted notation is shown in Table B-7 for easy reference. $P_{..}$ is equal to unity.

For passive smoking, we are interested only in correcting the c_{i0k} values that are for the observed never-smokers. It is assumed that the P_{hj}'s are the same for cases and controls

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(nondifferential misclassification). For given values of wife's subject status (i) and husband's smoking status (k), the correction when the wife's observed smoking status is "never" (j = 0), is:

$$C_{i0k} = c_{i0k} - \sum_{h=j=1}^{3} c_{ijk} \, (p_{h0} / p_{\cdot j}) \qquad \text{(B-1)}$$

where C_{i0k} is the corrected form of the element of the element c_{i0k}. Then the corrected passive risk, RR(c), becomes:

$$RR(c) = C_{101} \times C_{000} / C_{100} \times C_{001} \qquad \text{(B-2)}$$

The values of c_{0jk} in Table B-6 are from prevalence data in the study itself or from a related study, from concordance data, and from each study's data on the smoking prevalence of the never-smokers' husbands. If necessary, the number of former smokers can be estimated from the ever-smokers based on data from nine studies known to us where the percent of both current smokers and former smokers is known (see Table B-16). These data indicate a time trend in nontraditional societies, from 17% former smokers relative to ever-smokers in 1960 to 45% in 1985; we estimate a 20-year lag for the traditional societies such as Hong Kong, China, Japan, and Greece. However, there are no data to support this assumption.

To calculate the individual elements, c_{0jk}, of Table B-6, it is necessary to establish concordance factors--that is, the cross products in 2 x 2 tables of smoking status of husbands and wives by smoking level of the wives. Using data from Sutton (1980), Lee (1987b), Akiba et al. (1986) and Hirayama (1984) and the detailed data in Lee (1987b) on never-smokers, current smokers, and former smokers, we have calculated that an appropriate average concordance factor for current smoking wives and ever-smoking husbands versus never-smoking wives and never-smoking husbands is 3.2; for ever-smoking wives and husbands versus never-smoking wives and husbands, it is 2.8, and for former smoking wives and ever-smoking husbands versus never-smoking wives and husbands, it is 2.2. These concordance factors can be expected to vary from study to study, but the effect of the variability should tend to cancel out as the studies are aggregated. The element $c_{00\cdot}$ and a quantity $s_0 = \sum_{j=1}^{3} c_{0j\cdot}$

are obtained from smoking prevalence data in the study itself, in a related study on the same cohort, or as a last resort from national statistics. The elements c_{01}. and $c_{02}. + c_{03}.$ are taken from the study or are estimated from Table B-16. Element c_{02}. is estimated to be 10% of $(c_{02}. + c_{03}.)$; c_{03}. is 90%. Elements c_{000} and c_{001} are obtained from c_{00}. and the proportion of never-smoking controls in the study who are married to either never-smokers or ever-smokers. Elements c_{010} and c_{011} are obtained by solving the equations $c_{010} + c_{011} = c_{01}$. and $c_{000} \times c_{011} / c_{001} \times c_{010} = 2.2$. Terms $s_{00} = \sum_{j=1}^{3} c_{0j0}$ and $s_{01} = \sum_{j=1}^{3} c_{0j1}$ are obtained from the equations $s_{00} + s_{01} = s_0$ and $s_{01} \times c_{000}/c_{001} \times s_{00} = 2.8$. Then $c_{020} + c_{030} = s_{00} - c_{010}$ and $c_{021} + c_{031} = s_{01} - c_{011}$. The values of c_{020} and c_{021} are then assumed to be 10% of $c_{020} + c_{030}$ and $c_{021} + c_{031}$, respectively, and c_{030} and c_{031} are assumed to be 90%.

To obtain the elements for the subject cases ($i = 1$) in Table B-6, it is necessary first to set up relative risks for the passively exposed ($k = 1$) and not passively exposed ($k = 0$) wives by observed smoking status ($j = 0,1,2,3$). These risks are shown in Table B-8.

In most instances, the relative risk, RR(e), for female ever-smokers can be obtained from the study itself or from a related paper (Table B-9). In a few instances, it is necessary to estimate RR(e) from other studies similar in time and locale. In some papers, a current smoker risk also is given. We assume (based on cotinine measurements) that the misclassified regular smoker risk, $RR(a)_3$, is equal to the self-reported current smoker risk. Where only RR(e) is available, $RR(a)_3$ can be assumed to be equal to $1.24 \times RR(e)$ based on the data in Table B-17. Because occasional smokers have cotinine levels that are 10% to 30% of those of regular smokers, it is assumed that $RR(a)_2 - 1 = 0.20(RR(a)_3 - 1)$, and because the former smokers ($j = 1$) are said to be, on average, long term (Wald et al., 1986; Lee, 1987b), we have averaged the data of Alderson et al. (1985), Lubin et al. (1984), and Garfinkel and Stellman (1988) for 10+ year former smokers, namely, that $RR(a)_1 - 1 = 0.09\ (RR(a)_3 - 1)$.

The elements RR_{00} and RR_{01} are obtained from the observed passive relative risk in the study and the never-smoking population weights for controls in Table B-6 by solving the equations

$$(RR_{00} \times c_{000}) + (RR_{01} \times c_{001}) = 1.00$$

and

$$RR_{01} / RR_{00} = RR(p)_0.$$

Other assumptions regarding passive risks can be used for $j = 1,2,$ and 3. We have assumed, based on the data in Varela (1987) who found that 242 long-term former smokers had essentially the same passive risk as 197 never-smokers, that the passive risk for former smokers to be the same as for never-smokers, namely, that $RR(p)_1 = RR(p)_0$. It is also assumed that there is no passive risk for current or occasional smokers so $RR(p)_2$ and $RR(p)_3$ are unity.

Crude versions of the elements c_{1jk} ($i = 1$ for cases) are obtained by multiplying each element c_{0jk} by its respective RR_{jk}. These are then normalized to give

$$c_{1jk} = \frac{c_{0jk}RR_{jk}}{\sum_{j=0}^{3}\sum_{k=0}^{3} c_{0jk}RR_{jk}}$$

The next step is to set up Table B-7, which is the table of proportionate distribution. This is done by multiplying the observed misclassification rates ($P_{h0}/P_{\cdot j}$) from footnotes 2 and 4 in Tables B-3 and B-4, respectively, by the appropriate elements from Table B-6. For example, $P_{10} = C_{01}.(P_{10}/P_{\cdot 1})$. An attempt was made to use the true misclassification rates from Tables B-3 and B-4 on the theory that they would exhibit less variability in being transferred from the cotinine and discordant answer studies to the passive smoking calculations. However, the method is laborious and, as is shown in the Correa example below, does not lead to increased accuracy.

The next step is to develop a deletions table to implement Equation B-1, above, using the control and case smoking prevalences in Table B-6 and the proportionate distribution in Table B-7. Each observed element, c_{i0k}, in Table B-6 is multiplied by its appropriate observed misclassification factor, $P_{h0} / P_{\cdot j}$, where $h = j$, to yield a deletion element to be subtracted from the appropriate observed wives' never-smoking-status elements: c_{000}, c_{001}, c_{100}, and c_{101}, to obtain corrected elements C_{000}, C_{001}, C_{100} and C_{101}. Thus, $C_{000} = c_{000} - \sum_{h=j=1}^{3} c_{0j0}\, P_{h0}/P_{\cdot j}$, etc.

Once these corrected never-smoker elements are obtained, the relative risk corrected for smoker misclassification is obtained from Equation (B-2); $RR(c)_0 = C_{101} \times C_{000}/C_{100} \times C_{001}$, and the bias becomes $RR(p)_0 / RR(c)_0$.

B.6. NUMERICAL EXAMPLE

Using the Correa study as an example, the study tells us that 52.8% of the wives never smoked and that 45.9% of the never-smoking wives were exposed to their spouses' smoke. This establishes $c_{00\cdot}$ as 0.528 and c_{000} and c_{001} as 0.286 and 0.242, respectively. The quantity $s_{0\cdot}$, the proportion of ever-smokers, by difference is 0.472. Assuming (from Table B-16) that the former smokers are 35.5% of the ever-smokers, the former smokers, $c_{01\cdot}$, become 0.167, and the current smokers ($c_{02\cdot} + c_{03\cdot}$) become 0.305. The current smokers are divided into current regular smokers at 90% ($c_{03\cdot} = 0.275$) and current occasional smokers at 10% ($c_{02\cdot} = 0.030$). These data are shown in the bottom line of Table B-10.

Using the concordance factor of 2.8 for ever-smokers versus never-smokers, it is possible to show algebraically that 33.2% of the females in the Correa study would be ever-smoker wives with smoking husbands (s_{01}) and that 14.0% would be ever-smoker wives with never-smoking husbands (s_{00}). Similarly, using the concordance factor of 2.2 for former smoking wives and ever-smoking husbands versus the never-smokers, the former smoking wives married to ever-smoking husbands (c_{011}) would be 10.9% of the total and those married to the never-smoking husbands (c_{010}) would be 5.8%. Then by difference, exposed current smoking wives ($c_{021} + c_{031}$) would be 22.3%, to be split into 20.1% regular smokers (c_{031}) and 2.2% occasional smokers (c_{021}), and the nonexposed current smoking wives ($c_{020} + c_{030}$) would be 8.2%, split into 7.4% regular smokers (c_{030}) and 0.8% occasional smokers (c_{020}). These data now supply all the elements needed in Table B-10 and the control part of Table B-6.

The relative risk for passive smoking, $RR(p)_o$, for females is 2.07 (Correa et al., 1983). The age- and sex-adjusted relative risk for current smoking from a related paper (Correa, 1984) is 12.6. The ratio of female smoking crude risk to the average for males and females is about 80%, indicating an age-adjusted current female risk of about 10. (Note: This is different from the current smoker relative risk that would be calculated from the crude ever-smoker risk of 12.4 used in Table 5-7 [of this report] and Table B-3. The adjusted risk is used here simply as an example.) With these inputs and the weights of controls in the study, the various exposed and nonexposed relative risks are those shown in Table B-11. The weighted average risk for the occasional smokers is calculated as 0.20 (current regular risk - 1) + 1, which for this example is 0.20 (10 - 1) + 1 = 2.80. The weighted average risk for former smokers is 0.09 (current regular risk - 1) + 1, which is 0.09 (10 - 1) + 1 = 1.81. The weighted average risks are split between never-smoking and ever-smoking husbands by

using the passive risks and the population weights. A crude case prevalence table is then made up (Table B-12) by multiplying each c_{0jk} by its respective RR_{jk}. This table is then normalized by dividing through by 3.665 to yield Table B-13, which is the lower half of Table B-6 for this example.

The proportionate distribution table (Table B-14) is developed, as described above, from the misclassification factors in Tables B-3 and B-4 and the bottom line of Table B-10. For example, to arrive at element (h = 3, j = 0) the observed $P_{\cdot 3}$ of 0.275 is multiplied by an observed misclassification factor of 0.0102 (from Table B-3 of this report) to yield 0.00281, which rounds to 0.003. To explore the value of using the true misclassification factors instead of the observed ones, the true and observed m's were carried to five decimal places. An approximation procedure to determine the true smoking probabilities $P_{0\cdot}$, $P_{1\cdot}$, $P_{2\cdot}$, and $P_{3\cdot}$ was carried through four stages. The resulting total true distribution of smoking status, 0.49987, 0.18040, 0.03893, and 0.28081, rounded to three decimal places is essentially identical to the distribution shown in the bottom line of Table B-14. Similarly, any differences in the individual elements were very small and beyond the accuracy of the underlying data. The Correa study was chosen as our example because the female ever-smoking prevalence is reasonably high (47.2%) and the female current smoker lung cancer relative risk is high (10), both factors that should lead to a greater rather than a smaller correction to the passive risk.

We now can set up a deletions table, Table B-15, which is the equivalent of Equation 1 above, by multiplying the control and case elements in Table B-10 and B-13 by the appropriate observed misclassification rates $P_{h0} / P_{\cdot j}$ (h = j), namely, $P_{10}/P_{\cdot 1} = 0.117$, $P_{20} / P_{\cdot 2} = 0.196$, and $P_{30} / P_{\cdot 3} = 0.01020$. For example, to get 0.00678, one multiplies 0.058 from Table B-10 by 0.117. Then the first three columns are summed horizontally to get the fourth column which is then subtracted from the elements in the "never" columns of Tables B-10 and B-13 (column 5) to get the "corrected never" elements (column 6).

The corrected passive risk is now obtained by taking the cross product from the "corrected never" column: 0.07516 x 0.27690/0.04705 x 0.22308 = 1.984, which is to be compared with the observed risk of 2.07. The bias is then 2.07/1.984 = 1.044. It is interesting to note how sensitive the bias is to the smoker relative risk that is assumed. When the crude smoker risk (no age adjustment) of 12.4 for ever-smokers, equivalent to about 15.4 for current regular smokers, is assumed, the corrected passive risk is 1.90, and the basis is twice as great at 1.09.

Table B-1. Observed ratios of occasional smokers to current smokers (based on cotinine studies)

Study	Females			Both Sexes[3]		
	Occ'l	Current	Occ'l/Current	Occ'l[1]	Current	Occ'l Current
Lee (1986)	4	72	0.056	12	176	0.068
Coultas et al. (1988)				59	278	0.212
Haddow et al. (1986)	10	64	0.156			
Feyerabend (1982)[2]				7	82	0.085
Jarvis (1987)				12	90	0.133
Pojer (1984)				25	187	0.134
Wald et al. (1984)				13	131	0.099
Overall	14	136	0.103	128	944	0.136

[1] Occasional smokers are defined as persons who have cotinine levels in body fluids that are between 10% and 30% of the mean of all self-reported current smokers.
[2] The Feyerabend (1982) data are for nicotine.
[3] The "Both Sexes" data are shown to indicate that the female value of 10.3% is not unduly high.

Table B-2. Differences in smoker misclassification bias between EPA estimates and those of P.N. Lee regarding passive smoking relative risks for females

Study	% of U.S. Weight	Lee (1991 Model)[1]			Wells-Stewart Model					
		Lee (1991) Input Parameters			Lee (1991) Input[2] Parameters			EPA Input Parameters (Table 5-7)[2]		
		RR_o	RR_c	Bias	RR_o	RR_c	Bias	RR_o	RR_c	Bias
FONT	35	1.32	1.17	1.13	1.32	1.14[3]	1.15	1.29	1.26[3]	1.03
GARF (Coh)	25	1.17	1.02	1.15	1.17	0.99[4]	1.19	1.17	1.15[4]	1.02
GARF	15	1.23	1.09	1.13	1.23	1.06[5]	1.17	1.31	1.24[5]	1.06
JANE	10	0.75	0.65	1.15	0.75	0.62[6]	1.22	0.86	0.78[6]	1.10
CORR	3	2.07	1.63	1.26	2.07	1.47[7]	1.41	2.07	1.90[7]	1.09

Note: Calculated bias is very sensitive to three key factors, high values of which will drive the bias up; namely, fraction of observed never smokers misclassified, female active smoker relative risk and female smoking prevalence. Lee's inputs are higher than EPA's as indicated in footnotes 2-7. RR_o = observed passive risk. RR_c = passive risk corrected for smoker misclassification bias. Bias = RR_o/RR_c.

[1] Multiplicative model, Lee's Table 3.

[2] EPA's misclassification factors developed in Section B.4., namely, 1.02% of current regular smokers, 19.6% of current occasional smokers, and 11.7% of ex-smokers, when weighted for their respective prevalence and relative risk, are equivalent to about 1.5% of average self-reported ever smokers. EPA used these rates for all studies except FONT which is a special case. Lee used 2.0% for all studies.

[3] All current smokers, regular plus occasional, were eliminated from the analysis based on cotinine test data. This results in a misclassification factor of 0.5% of ever smokers. Lee's 49% ever smokers is higher than 1985 U.S. statistics value of 42%.

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Table B-2. (continued)

[4] A female smoker risk of 3.58 (U.S. DHHS, 1986) and smoker prevalence of 32% (Hammond, 1966) are considered standard for this study. Lee used 8.0 and 49%.

[5] EPA estimates a smoker risk of 6 and a smoking prevalence of 46% for the time period 1971-81 vs. Lee's values of 8.0 and 49%.

[6] The main difference is in the assumed smoker misclassification rate but Lee's assumption of 49% smoking prevalence vs. 46% assumed by EPA increases the bias estimate by about 3%.

[7] Lee assumed 58% smoking prevalence vs. 47% which EPA got from the paper itself. Lee assumed a lower smoker risk (9.5) vs. EPA's 12.4; the effect of this was offset by Lee's assumption of a multiplicative model for smoker's passive risk vs. EPA's assumption of no passive risk for smokers.

Table B-3. Misclassification of female current smokers

		Self-reported Smoking Status		
Study	Cotinine Level[1]	Never[2]	Former[2]	Current
Coultas et al. (1988)	10-30	7	3	
	30+	5	8	
	All	387	79	184
Cummings (1990)	10-30	0	1	
	30+	2	0	
	All	225	143	116
Pierce et al. (1987)	10-30	9	4	
	30+	3	3	
	All	232	79	167
Subtotal	10-30	16	8	(67% never)
	30+	10	11	(48% never)
	All	844	301	467
Lee (1986)[3]	10-30	3	2	
	30+	2	3	
	All	333	125	256
Haddow et al. (1986)[3]	10-30	1	1	
	30+	0	1	
	All	174	58	64
Haddow et al. (1988)[3]	10-30	8	4	
	30+	1	0	
	All	1,128	380	503
Riboli (1991)[3]--US[4]	10-30	1	0	
	30+	0	0	
	All	224	81	143
Riboli (1991)[3]--East Asia[5]	10-30	1	1	
	30+	1	0	
	All	325	25	77
Riboli (1991)[3]--Greece[6]	10-30	0	0	
	30+	0	0	
	All	96	5	15
Total	10-30	30	16	
	30+	14	15	
	All	3,124	975	1,525

Table B-3. (continued)

[1] Cotinine levels are in units of percents of the mean of self-reported smokers for each study; 30+% are defined as current regular smokers, 10-30% are occasional smokers.

[2] The observed current smokers are assumed to be 90% regular (1,372) and 10% occasional (153) smokers. For regular smokers, misclassification as never-smokers is 14/372 = 1.02% of observed current regulars or 14/(1,372 + 14 + 15) = 1.00% of true current regulars. For occasional smokers, misclassification is 30/153 = 19.6% of observed current occasionals or 30/(153 + 30 +16) = 15.1% of true current occasionals. For current smokers misclassified as former smokers the factors are 15/1,372 = 1.09% for observed and 15/1,401 = 1.07% for true regular smokers, and 16/153 = 10.5% for observed and 16/199 = 8.0% for true occasionals.

[3] For Lee (1986), Haddow et al. (1986), Haddow et al. (1988), and Riboli (1991), there was no breakdown given between "Never" and "Former", because the numbers are small, an estimate was made based on the subtotal distribution. The number of smokers had to be estimated in some cases.

[4] New Orleans, Los Angeles, and Honolulu.

[5] China (Shanghai), Hong Kong, and Japan (Sendai).

[6] Athens.

Table B-4. Misclassification of female former smokers reported as never-smokers based on discordant answers

Study	Locale	Former Smokers (FS)[1]	Ever-Smokers (ES)[1]	Reported never-smokers who reported earlier that they had smoked[1]		
				N	Percent of ES	Percent of FS
Kabat and Wynder (1984)[5]	U.S.					
Controls		109	319	0	0.0	0.0
Cases		222	652	7	1.1	3.2
Machlin et al. (1989)	U.S.	194	687	52	7.6	26.8
Krall et al. (1989)[2]	Mass.	11	30	1	3.3	9.1
Britten (1988)[3]	U.K.	320	878	38	4.3	11.9
Lee (1987b)	U.K.	85	243	13	5.5	15.3
Akiba et al. (1986)	Japan	8	38	0	0.0	0.0
Overall[4]		949	2847	111	3.9	11.7

[1] Number of former smokers and ever-smokers had to be estimated in some cases.
[2] Krall data are based on 20-year recall.
[3] Britten data include only those persons who said they never smoked but actually had smoked regularly one or more cigarettes per day.
[4] For former smokers, misclassification as never-smokers would appear to be 111/949 = 11.7% of observed former smokers or 111/(949 + 111) = 10.5% of true former smokers, but from Table B-3 16 + 15/(16 + 15 + 975) = 3.08% of former smokers are really current smokers, so the 949 + 111 = 1,060 should be reduced by 3.08% to 1,027 as the number of true former smokers. Then 111/1,027 = 10.81% based on true former smokers.
[5] Dr. Kabat (private communication) advised that of 13 misclassifieds, 8 were females, 1 of whom used snuff.

Table B-5. Misclassification of female lung cancer cases

Source	Number of Ever-smokers	Number Misclassified
CHAN Chan et al. (1979)[1]	12	1
KABA Kabat and Wynder (1984)[2]	652	7
AKIB Akiba et al. (1986)	38	0
PERS Pershagen et al. (1987)	179	2
HUMB Humble et al. (1987)[3]	223	1
Total	1,104	11 (1%)
General Population[4]	1,838	104 (5.7%)

[1] Chan sampled five Type I and II never-smokers, one of whom was said by a relative to have smoked a few hand-wrapped cigarettes for a year at age 71. The ratio of smoking to nonsmoking cases for Types I and II was 44/19, which, multiplied by 5, leads to 12 estimated ever-smokers.
[2] Dr. Kabat (private communication) advised that of 13 misclassifieds, 8 were females, 1 of whom used snuff.
[3] Of the four misclassifieds found, Dr. Humble (private communication) has advised that most if not all were males. We have assumed one female.
[4] The general population data are taken from the four nonlung cancer cohorts in Table B-4, namely, Machlin (1989), Krall (1989), Britten (1988), and Lee (1987b).

Table B-6. Notation for proportionate distribution of reported female lung cancer cases and controls by husband's smoking status

		Wife's Observed Smoking Status (j)				
Wife's Subject Status (i)	Husband's Smoking Status (k)	Never (j = 0)	Ex (j = 1)	Occ'l (j = 2)	Reg (j = 3)	Total
Control	Never (k = 0)	c_{000}	c_{010}	c_{020}	c_{030}	$c_{0\cdot 0}$
(i = 0)	Ever (k = 1)	c_{001}	c_{011}	c_{021}	c_{031}	$c_{0\cdot 1}$
	Total	$c_{00\cdot}$	$c_{01\cdot}$	$c_{02\cdot}$	$c_{03\cdot}$	$c_{0\cdot\cdot}$ (= 1)
Case	Never (k = 0)	c_{100}	c_{110}	c_{120}	c_{130}	$c_{1\cdot 0}$
(i = 1)	Ever (k = 1)	c_{101}	c_{111}	c_{121}	c_{131}	$c_{1\cdot 1}$
	Total	$c_{10\cdot}$	$c_{11\cdot}$	$c_{12\cdot}$	$c_{13\cdot}$	$c_{1\cdot\cdot}$ (= 1)

Table B-7. Proportionate distribution notation for subjects by observed and true smoking status

Wife's Observed Smoking Status (j)	Wife's True Smoking Status (h)				
	Never (h = 0)	Former (h = 1)	Occ'l (h = 2)	Reg. (h = 3)	Total
Never (j = 0)	P_{00}	P_{10}	P_{20}	P_{30}	$P_{\cdot 0}$
Former (j = 1)	P_{01}	P_{11}	P_{21}	P_{31}	$P_{\cdot 1}$
Occ'l (j = 2)	P_{02}	P_{12}	P_{22}	P_{32}	$P_{\cdot 2}$
Reg. (j = 3)	P_{03}	P_{13}	P_{23}	P_{33}	$P_{\cdot 3}$
Total	$P_{0\cdot}$	$P_{1\cdot}$	$P_{2\cdot}$	$P_{3\cdot}$	$P_{\cdot\cdot}(= 1)$

Table B-8. Observed lung cancer relative risks for exposed and nonexposed wives by the wife's smoking status using average never-smoking wives as the reference category

	Wife's Smoking Status			
Husband's Smoking Status	Never ($j = 0$)	Former ($j = 1$)	Occ'l ($j = 2$)	Reg. ($j = 3$)
Never ($k = 0$)	RR_{00}	RR_{10}	RR_{20}	RR_{30}
Ever ($k = 1$)	RR_{01}	RR_{11}	RR_{21}	RR_{31}
Weighted avg. active risk	$RR(a)_0 = 1.00$	$RR(a)_1$	$RR(a)_2$	$RR(a)_3$
Passive risk[1] $RR(p)_j = RR_j1/RR_{j0}$	$RR(p)_0$	$RR(p)_1$	$RR(p)_2$	$RR(p)_3$

[1] Observed passive risk--the ratio of the exposed risk to the unexposed risk in each column.

Table B-9. Prevalences and estimates of lung cancer risk associated with active and passive smoking[33]

	Ever-smokers		Never-smokers		
Case-Control	Prev. (%)[1]	Crude RR[2]	Prev. of Exposed (%)[3]	Crude RR[2,17]	Adj. RR[2,4,17]
AKIB	21	2.38 (1.67, 3.39)	70	1.52 (0.96, 2.41)	**1.5 (1.0, 2.5)**
BROW	29	4.30[23] (2.24, 8.24)	15	**1.52[23] (0.49, 4.79)**	*
			12	1.82[23] (0.45, 7.36)[7]	1.68[23] (0.39, 6.90)[7]
BUFF	59	7.06[15] (5.18, 9.63)	84	**0.81[15] (0.39, 1.66)**	*
CHAN	26	3.48 (2.42, 4.99)	47	**0.75 (0.48, 1.19)**	*
CORR	47	12.40 (8.35, 18.4)	46	**2.07[24] (0.94, 4.52)**	*
FONT[34]	42[21]	8.0[21]	63	1.37 (1.10, 1.69)	**1.29 (1.03, 1.62)**
			66	1.21 (0.94, 1.56)	1.28 (0.98, 1.66)
			64	1.32 (1.08, 1.61)	*
GAO	18	2.54 (2.06, 3.12)	74	**1.19 (0.87, 1.63)**	1.34[5,6]
GARF	*	*	61	**1.31 (0.93, 1.85)**	1.70[26] (0.98, 2.94)[7]
GENG	41	2.77[27] (1.89, 4.07)	44	**2.16** (1.21, 3.84)	*
HIRA[8]	16	3.20[9] (2.67, 3.83)	77	**1.53[5] (1.10, 2.13)**	1.64[5] *
HUMB	41	16.3 (10.5, 25.1)	56	2.34 (0.96, 5.69)	**2.2 (0.9, 5.5)**
INOU	16	1.66 (0.73, 3.76)	64	**2.55[16] (0.90, 7.20)**	2.54[5,10] *

Table B-9. (continued)

	Ever-smokers		Never-smokers		
Case-Control	Prev. (%)[1]	Crude RR[2]	Prev. of Exposed (%)[3]	Crude RR[2,17]	Adj. RR[2,4,17]
JANE	46[21]	8.0[21]	80	**0.86 (0.57, 1.29)**	0.93/0.44[11]
KABA[28]	42	5.90 (4.53, 7.69)	60	**0.79 (0.30, 2.04)**	*
KALA	17	3.32 (2.12, 5.22)	60	1.62[12] (0.99, 2.65) 1.41 (0.78, 2.55)	**1.92 (1.02, 3.59)**[7] *
KATA	28	1.21 (0.50, 2.90)	82	*[19]	*
KOO	32	2.77 (1.96, 3.90)	49	**1.55 (0.98, 2.44)**	1.64
LAMT	24	3.77 (2.96, 4.78)	45	**1.65 (1.22, 2.22)**	*
LAMW	22	4.12 (2.79, 6.08)	56	**2.51**[20] **(1.49, 4.23)**	*
LEE	60[29]	4.61[29]	68	**1.03 (0.48, 2.20)**	0.75/1.60[13]
LIU	0.05	*	87	0.74 (0.37, 1.48)	**0.77 (0.35, 1.68)**
PERS	37[21]	4.2[21]	43	1.28 (0.82, 1.98)	**1.2 (0.7, 2.1)**[7]
SHIM	21[21]	2.8[21]	56	**1.08**[30] **(0.70, 1.68)**	*
SOBU	21	2.81 (2.22, 3.57)	54	1.06[12] (0.79, 1.44) 1.77 (1.29, 2.43)	1.13[12] (0.78, 1.63)[7] **1.57 (1.07, 2.31)**[7]
SVEN	43	5.97 (4.11, 8.67)	66	**1.26**[14] **(0.65, 2.48)**	1.4[14]
TRIC	10	2.81[25] (1.69, 4.68)	52	**2.08**[25] **(1.31, 3.29)**	*

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Table B-9. (continued)

	Ever-smokers		Never-smokers		
Case-Control	Prev. (%)[1]	Crude RR[2]	Prev. of Exposed (%)[3]	Crude RR[2,17]	Adj. RR[2,4,17]
WU	58	4.38 (2.97, 6.47)	60	**1.41[18] (0.63, 3.15)**	1.2 (0.6, 2.5)[7]
WUWI	37	2.24 (1.92, 2.62)	55	**0.79 (0.64, 0.98)**	0.7
BUTL (Coh)	14[21]	4.0[21]	*	2.45[31]	**2.02 (0.48, 8.56)[7]**
GARF (Coh)	33[22]	3.5[22]	72	*	**1.17[5] (0.85, 1.61)[7]**
HIRA (Coh)	16	3.20[9] (1.96, 3.90)	77	**1.38 (1.03, 1.87)**	1.61 *
HOLE[32] (Coh)	56	4.2[21]	73	2.27 (0.40, 12.7)	**1.99 (0.24, 16.7)[7]**

1 Percent ever-smokers in controls of whole study (or parent study).

2 Parentheses contain 90% confidence limits, unless noted otherwise. Crude ORs and their confidence limits were calculated by the reviewers wherever possible. Boldface indicates values used for analysis in text of this report. OR for case-control studies; relative risk (RR) for cohort studies. The reference category for active smoking is all never-smoking, for passive smoking, it is unexposed never-smokers.

3 Percent of never-smoking controls exposed to spousal smoking, unless noted otherwise.

4 Calculated by a statistical method that adjusts for other factors (see Table 5-5).

5 Composite measure formed from categorical data at different exposure levels.

6 For Gao, data are given as (number of years lived with a smoker, adj. OR): (< 20, 1.0), (20-29, 1.1), (30-39, 1.3), (40+, 1.7).

7 95% confidence interval.

8 Case-control study nested in the cohort study of Hirayama. OR for ever-smokers is taken from cohort study (shown in table below). This case-control study is not counted in any summary results where HIRA(Coh) is included.

9 Crude OR is calculated from prospective data in Hirayama (1988). Adjusted OR for ever-smokers given there is 2.67 (no confidence interval [C.I.]).

10 For Inoue, data are given as (number of cig./day smoked by husband, adj. OR): (< 19, 1.58), (20+, 3.09).

11 From subject responses/from proxy responses.

12 For the first value, "ETS exposed" means the spouse smokes; for the second value, "ETS exposed" means a member of the household other than the spouse smokes.

13 From subject responses/from spouse responses.

14 Exposure at home and/or at work.

Table B-9. (continued)

[15] Exposure to regularly smoking household member. Differs slightly from published value of 0.78, wherein 0.5 was added to all exposure cells.

[16] OR reported in study is 2.25, in contrast to the value shown that was reconstructed from the confidence intervals reported in the study; no reply to inquiry addressed to author had been received by press time.

[17] ORs for never-smokers applies to exposure from spousal smoking, unless indicated otherwise.

[18] Raw data for WU is from Table 11 of the Surgeon General's report (U.S. DHHS, 1986). Data apply to adenocarcinoma only.

[19] Odds ratio is not defined because number of unexposed subjects is 0 for cases or controls.

[20] Table entry is for exposure to smoking spouse, cohabitants, and/or coworkers; includes lung cancers of all cell types. The OR for spousal smoking alone is for adenocarcinoma only: 2.01 (90% C.I. = 1.20, 3.37).

[21] From other studies similar in location and time period (see Table 5-7).

[22] Prevalence is calculated from figures in Stellman and Garfinkel (1986) and includes all women except those who "never smoked regularly." RR is from U.S. Surgeon General (U.S. DHHS, 1982).

[23] Adenocarcinoma only. Data and OR value communicated from author (Brownson).

[24] Excludes bronchioalveolar carcinoma. Crude OR with bronchioalveolar carcinoma included is reported to be 1.77, but raw data for calculation of confidence interval are not provided.

[25] Known adenocarcinomas and alveolar carcinomas were excluded, but histological diagnosis was not available for many cases. Data are from Trichopoulos et al. (1983).

[26] Estimate for husband smoking 20 cigarettes per day.

[27] Crude OR reported in study is 3.05 (95% C.I. = 1.77, 5.30); adjusted OR is 2.6(95% C.I. = 1.4, 4.6).

[28] For second KABA study (see addendum in study description of KABA), preliminary unpublished data and analysis based on ETS exposure in adulthood indicate 68% of never-smokers are exposed and OR = 0.90 (90% C.I. = 0.51, 1.58), not dissimilar from the table entry shown.

[29] From Alderson et al. (1985).

[30] From crude data estimated to be the following: exposed cases 52, exposed controls 91, unexposed cases 38, unexposed controls 72.

[31] RR is based on person-years of exposure to spousal smoking. Prevalence in those units is 20%.

[32] RR values under never-smoker are for lung cancer mortality. For lung cancer incidence, crude RR is 1.51 (90% C.I. = 0.41, 5.48) and adj. RR is 1.39 (95% C.I. = 0.29, 6.61).

[33] Values used for inference in this report are shown in boldface. * means no information available.

[34] The first, second, and third entries are calculated for population controls, colon cancer controls, and both control groups combined, respectively. For adenocarcinoma alone, the corresponding ORs, both crude and adjusted, are higher by 0.15 to 0.18.

Table B-10. Observed smoking prevalence among the controls--Correa example

Husband's Smoking Status	Wife's Smoking Status				
	Never	Former	Occasional	Regular	All
Never	0.286	0.058	0.008	0.074	0.426
Ever	0.242	0.109	0.022	0.201	0.574
All	0.528	0.167	0.030	0.275	1.000

Table B-11. Observed relative risks--Correa example

Husbands' Smoking Status	Wife's Smoking Status			
	Never (j = 0)	Former (j = 1)	Occasional (j = 2)	Regular (j = 3)
Never	0.67	1.07	2.80	10.0
Ever	1.39	2.21	2.80	10.0
Weighted Average	1.00	1.81	2.80	10.0
Passive Risk, $RR(p)_j$	2.07	2.07[1]	1.00[1]	1.00[1]

[1] Assumed.

Table B-12. Crude case table - prevalence of cases by smoking status--Correa example

	Wife's Smoking Status				
Husband's Smoking Status	Never	Former	Occasional	Regular	All
Never	0.192	0.062	0.022	0.740	1.016
Ever	0.336	0.241	0.062	2.010	2.649
All	0.528	0.303	0.084	2.750	3.665

Table B-13. Normalized case table - prevalence of cases by smoking status--Correa example

	Wife's Smoking Status				
Husband's Smoking Status	Never	Former	Occasional	Regular	All
Never	0.052	0.017	0.006	0.202	0.277
Ever	0.092	0.066	0.017	0.549	0.723
All	0.144	0.083	0.023	0.750	1.000

Table B-14. Proportionate distribution of observed and true smoking status for wives in Correa example[1]

Wife's Observed Smoking Status	Wife's True Smoking Status: Never (h = 0)	Former (h = 1)	Occasional (h = 2)	Regular (h = 3)	All
Never (j = 0)	0.500	0.020	0.006	0.003	0.528
Ex (j = 1)	0	0.161	0.003	0.003	0.167
Occ'l (j = 2)	0	0	0.030	0	0.030
Regular (j = 3)	0	0	0	0.275	0.275
All	0.500	0.180	0.039	0.281	1.000

[1] Values rounded to three decimal places.

Table B-15. Deletions from the never columns in Tables B-10 and B-13

Husband's Smoking Status		Wife's Smoking Status Former (1)	Occ'l (2)	Regular (3)	Sum[1] (4)	Observed Never (5)	Corrected Never[2] (6)
Table B-10 (pop.)	Never	0.00678	0.00157	0.00075	0.00910	0.286	0.27690
	Ever	0.01274	0.00433	0.00205	0.01892	0.242	0.22308
Table B-13 (cases)	Never	0.00198	0.00120	0.00206	0.00524	0.05229	0.04705
	Ever	0.00769	0.00331	0.00559	0.01659	0.09178	0.07519

[1] (4) = (1) + (2) + (3)
[2] (6) = (5) - (4)

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Table B-16. Observed ratios of female former smokers to ever-smokers in the U.S.A., U.K., and Sweden: populations or controls (numbers or %)

Study	Time Frame	Never-Smokers	Current Smokers	Former Smokers	Ever-Smokers	Former/Ever-Smokers
Hammond (1966)	1960	381,369	150,017	31,285	181,302	0.17
Buffler et al. (1984)	1978	41%	38%	21%	59%	0.36
Wu et al. (1985)	1980	92	73	55	128	0.43
Lee (1987b)	1980	48.3%	33.6%	18.1%	51.7%	0.35
Brownson et al. (1987)	1980	47	11	8	19	0.42
Britten (1988)	1982	767	558	320	878	0.36
Humble et al. (1987)	1982	162	63	48	111	0.43
Svensson et al. (1989)	1984	120	53	36	89	0.40
Garfinkel and Stellman (1988)	1982	350,650	132,366	136,909	269,275	0.51

Assumed Ratios by Years (non-traditional societies)[1]

Year	1960	1965	1970	1975	1980	1985
Ratio	0.17	0.23	0.28	0.34	0.39	0.45

[1] Traditional societies (Japan, Greece, China, Hong Kong) are estimated to lag these ratios by about 20 years, although there are no data in the studies to confirm this. However, because the bias for the traditional societies is very low, changes in values of this parameter have little effect.

Table B-17. Observed ratios of current smoker lung cancer risk to ever-smoker risk for females

		Lung Cancer RR		Ratio
Study	Exposed Cases Plus Controls	Current Smoker	Ever-Smoker	Current Smoker RR/ Ever-smoker RR
Alderson et al. (1985)	901	4.5	4.75	0.95
Buffler et al. (1984)	701	7.9	6.9	1.15
Garfinkel and Stellman (1988)	832	12.7	8.35	1.52
Humble et al. (1985)	268	18.0	13.0	1.38
Svensson et al. (1989)	261	8.46	6.10	1.39
Wu et al. (1985)	317	6.5	4.4	1.48
Overall	3,280	8.05	6.52	1.24[1]

[1] The summary ratio of 1.24 is the log mean of the individual ratios weighted by the exposed cases plus controls in that study.

APPENDIX C

REVIEW FORMAT FOR CASE-CONTROL STUDIES

PART I GENERAL

Study name ____

Location ____

Time period (data collection) ____

Study objective(s) ____

____

____

The source of the primary data set is the current study ______ or a parent study

(ref) ____

containing CS (current) ______ FS (former) ______ NS (never-smoker) ______

Study uses term "nonsmoker" ______ or "never-smoker" ______ to mean

nonsmoker ____

____

never-smoker ____

____

"Exposed" to ETS means (preferably in terms of spousal smoking)

____

____

Recall span (how far back in time ETS-exposure was measured) ____________________

____

ETS sources include cigarette _______ cigar _________ pipe _______ other _______

Describe inclusion of non-smoking (never smoking) females not currently married (number of cases and controls, assumptions exposure)

____

____

____

II DATA COLLECTION (includes NS_______ FS_______ CS_______ unless noted)

Inclusion/Exclusion criteria

Cases______________________________________

____

____

Controls (include matching variables in PART V)______________

____

____

Main source of subjects	Cases	Controls
Hospital(s) #__________	______	______
Community	______	______
Other__________	______	______

Incident cases Y________ N________

Control sampling

Cumulative	______	Density	______
Unmatched	______	Matched	______

Method of collection	Cases	Controls
Face-to-face	______	______
Telephone	______	______
Self-admin. ques.	______	______
Medical records	______	______
Vital stat. records	______	______
Other__________	______	______

Collected data verified/corroborated with other sources Y________ N________

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	Cases	Controls
Sample size (prior to attrition)		
females	______	______
males	______	______
Attrition (selection or follow-up)		
females	______	______
males	______	______
Source of response		
subject	______	______
proxy	______	______

Exposure sources NS______ FS______ CS______

	Yes	No
Childhood	______	______
Adulthood	______	______
Spouse	______	______
Parents/in-laws	______	______
Other family/ live-ins	______	______
Workplace	______	______
Other	______	______

Age NS______ FS______ CS______

Distribution	Cases	Controls
______	______	______
______	______	______
______	______	______
______	______	______
Mean	______	______
Standard error	______	______
Standard deviation	______	______
Range	______	______

PART III CLINICAL DATA

Primary lung cancer verified by NS______ FS______ CS______

Histology	______
Cytology	______
Radiology/clinical	______

Death certificate ______
Tumor registry ______
Mortality records ______
Other____________ ______
Not verified ______

Airway proximity (no. exp cases/no. cases) NS_____ FS_____ CS_____

Central ____________________

Table__________

Peripheral ____________________

Tumor type (no. exp cases/no. cases) NS_____ FS_____ CS_____

Squamous cell ____________________

Table__________

Small cell ____________________

Adenocarcinoma ____________________

Large cell ____________________

Others or unspecified ____________________

PART IV STATISTICAL ANALYSIS (includes NS_____ FS_____ CS_____ unless noted)

Raw data (for analysis)

		Cases	Controls
females	unexp	______	______
	exp	______	______
males	unexp	______	______
	exp	______	______

Comments (include measure of exposure) Table __________

Unadjusted (crude) analysis

Estimate OR __________ __________% CI (__________,__________)

Comments Table ____________

Test of signif p-value ____________

Test for trend p-value ____________

Comments Table ____________

Adjusted analysis

Estimate OR __________ __________% CI (__________,__________)

Test of signif p-value ____________

Test for trend p-value ____________

Comments Table ____________

PART V DEPENDENT VARIABLES (potential confouders and effects modifiers considered)

	In Matching	In Analysis	Otherwise
Age			
Gender			
Race/ethnicity			
Hospital			
Residence/ neighborhood			
Housing type			
House/room sizes			
Vital statistics			
Smoking status			
SES			
Medical health			
Menstrual/ reproductive			
Occupation			
Outdoor air pollution			
Cooking habits			
Drinking			
Diet			

Education			
Family history of LC			
Other indoor smoke/fumes			
Radon			
Lifestyle			
Climate/ ventilation			

APPENDIX D. LUNG CANCER MORTALITY RATES ATTRIBUTABLE TO SPOUSAL ETS IN INDIVIDUAL EPIDEMIOLOGIC STUDIES

Many of the epidemiologic studies on lung cancer and environmental tobacco smoke (ETS) were part of larger investigations that included ever-smokers and never-smokers. For those studies, the lung cancer mortality rate (LCMR) for all causes, appropriate to the location and time period of the study, has been obtained from other sources. Those values and parameter estimates from the studies are used to partition the excess LCMR from all causes (i.e., the excess after allowance for baseline sources) into components attributable to ever-smokers (from current and former smoking) and never-smokers (from exposure to spousal ETS) and to estimate the LCMR in the subpopulations of interest--unexposed never-smokers (meaning not exposed to spousal smoking), exposed never-smokers (exposed to spousal smoking), and ever-smokers ("exposed" is not used to mean exposure to non-spousal ETS, which applies to the whole target population). The method is explained in Sections 6.3.1 and 6.3.2.

Lung cancer mortality rates for the case-accrual periods of case-control studies are displayed in Table D-1. For the studies that collected data on both ever-smokers and never-smokers, the parameter estimates used are shown in Table D-2. The value for the lung cancer mortality rate is from Table D-1, and the remaining estimates are from individual study data. For HIRA(Coh), the lung cancer mortality rate for the time and location of the nested case-control study HIRA is used. For GARF(Coh), the rate for GARF in 1971 is assumed, which is the approximate time of the cohort follow-up. These values may not be very "representative" for lung cancer mortality in these two cohort studies because they extended over several years, and the LCMRs changed from year to year, particularly in the United States. This same difficulty arises in choosing a "representative" year for lung cancer mortality in the case-control studies, although to a lesser degree. The most extreme examples are KABA, PERS, INOU, and GARF with case-accrual periods of 10 years or more.

The estimates of prevalence of ever-smokers and the percent of never-smokers exposed to spousal smoking are the observed proportions in the control group. The extent to which the control group is representative of the country's population differs between studies, with those most questionable shown in Table 5-14A. The study reviews in Appendix A provide more detailed information. The restriction of cell types among cases in some studies is another consideration. Active smoking is much more strongly associated with occurrence of squamous and small cell carcinoma than with large cell carcinoma and adenocarcinoma. FONT presents evidence that passive smoking is more associated with adenocarcinoma than with other cell types. As noted

in Table 5-15, some studies excluded candidate lung cancer cases of specific histopathological types. This may produce some bias and distortion of comparison between studies. For example, BROW includes only cases of adenocarcinoma, which should bias the relative risk of ever-smokers toward unity, thus attributing too little lung cancer mortality to active smoking and too much to passive smoking and background sources.

Of a more positive nature, there is some advantage to using data from a single study to assign attributable *fractions* to different causes. To estimate the yearly number of lung cancers from each cause, the fraction is multiplied by the LCMR for the location and time of the study; that figure has to be obtained from sources on vital statistics. As seen in Table D-2, the mortality rates from lung cancer vary considerably between and within countries. For example, the rates used for studies in the United States range between 9 and 26. Applying the lung cancer rate suitable to each individual study should provide better estimates for comparison within a country than using a single figure for the whole country for some specific year.

Despite the reservations described, partitioning the lung cancer mortality for each study into components attributable to ever-smoking, spousal ETS, and baseline sources (nontobacco smoke and nonspousal ETS) provides a broad overview worth noting. The calculated values are shown in Table D-3. Estimates of relative risk for exposure to spousal ETS (RR_2 in notation of Section 6.3.2) less than 1.0 (see Table 5-8) were replaced by 1.0 to avoid a negative LCMR attributable to spousal ETS and the consequent inflation of the LCMR attributable to baseline sources and ever-smoking. Aside from the studies for Hong Kong and China, estimates of lung cancer mortality due to background sources cluster in the interval 1.5 to 5.5 (excluding BROW, which is strongly biased), predominantly from 3 to 5. The values for Hong Kong and China, however, are much higher, ranging from 7 to 14.5. The presence of indoor sources of non-ETS encountered in some of the studies in China may be a factor, but there is no apparent explanation for the outcome in Hong Kong. Assuming that the background rate of lung cancer is much higher in Hong Kong (and possibly China) as it appears, then the question arises as to whether the high excess rate relative to other countries may be attributable to higher exposure to ETS aside from spousal smoking or whether it is more likely due to other causes. Summary data from the ten-country collaborative study of ETS exposure to nonsmoking women conducted by the International Agency for Research on Cancer (IARC) (Riboli et al., 1991) was kindly submitted to us for Hong Kong, Japan (Sendai), and the United States (Los Angeles, New Orleans) from Drs. L.C. Koo, H. Shimizu, A. Wu-Williams, and T.H. Fontham, respectively. The average cotinine/creatinine (ng/mg) levels for nonsmoking women who are not employed and not married to a smoker are close for Sendai, Los Angeles, and New Orleans, but they are several times higher

for Hong Kong. Consequently, a high contribution to background lung cancer mortality from ETS aside from spousal smoking cannot be eliminated as a factor.

The lung cancer attributable to ever-smoking, spousal smoking, and baseline sources depends on the population proportions for those categories as well as the relative risks. Study estimates of the LCMR in each category, in units of lung cancer deaths per 100,000 at risk per year, are shown in Table D-4. The last two columns show the ratios of the LCMR and the excess LCMR for exposed never-smokers to ever-smokers. As above, relative risk estimates of less than 1.0 were set to 1.0 for the calculations. There is considerable variability across study estimates, even within the same country, as observed previously in the relative risks for spousal smoking.

To summarize, for studies that included data on ever-smokers, the LCMR for all causes was partitioned by attributable source (Table D-3). Although there is considerable uncertainty in the estimates from statistical variability and other sources, the outcomes provide some useful gross comparisons. For example, the lung cancer mortality rates from all causes differ markedly between countries and also vary widely between studies within the United States. The proportion of lung cancers attributable to ever-smoking is very high in the United States, compared to some more traditional countries (e.g., Japan and Greece).

Individual study estimates of the number of lung cancer deaths per year per 100,000 of female population from exposure of never-smokers to spousal ETS are predominantly between 0 and about 2.5. Estimates of the LCMR attributable to baseline sources (nonspousal ETS and nonsmoking causes) are somewhat higher, largely between 2 and 5, except in Hong Kong and China, where they range between 7+ and 14. (The U. S. study denoted as BROW has a high value, but that should be upwardly biased because it used only cases of adenocarcinoma, which is not a common cell type in smokers.) For reasons discussed in Chapter 5, we would be reluctant to draw conclusions about China on the basis of the epidemiologic studies. The evidence from Hong Kong, however, is very suggestive that the lung cancer rate in women due to baseline sources is very high. The extent to which that is attributable to nonsmoking sources of lung cancer and/or high exposure to nonspousal ETS is not apparent. The cotinine data for Hong Kong from the ten-country IARC study (Riboli, 1990) is consistent with excessively high ETS exposure, so nonspousal ETS may be a factor.

Table D-1. Female lung cancer mortality from all causes in case-control studies[1]

Study	Location	Case Accrual	Begin	Average	End	Accrual -10 yrs Average	Accrual -20 yrs Average
AKIB	Japan	1971-80	5.13	6.05	7.08	4.57	2.30
BROW	USA	1979-82	15.68	17.29	19.09	9.49	4.75
BUFF	USA	1976-80	13.94	15.29	17.20	7.86	4.38
CHAN	HK	1976-77	23.59	23.59	23.59	19.05	*
CORR[2]	USA	1979-82	26.0	26.0	26.0	9.49	4.75
GAO[3]	China	1984-86	*	18.0	*	14.3[2]	5.1[2]
GARF	USA	1971-81	9.45	13.55	17.20	6.87	*
GENG[3]	China	1983	*	27.8	*	13.8[2]	*
HIRA[7]	Japan	1965-81	4.46	5.70	7.08	4.01	*
HUMB[2]	USA	1980-84	17.7	17.7	*	10.55	5.13
INOU	Japan	1973-83	5.55	6.53	7.46	4.93	2.95
JANE[2]	USA	1982-84	23.7	23.7	*	9.06	5.42
KABA[4]	USA	1961-80	4.69	13.20	17.20	6.61	4.16
KALA[4]	Greece	1987-89	6.58	6.58[4]	6.58	6.75	5.83[4]
KATA[4]	Japan	1984-87	*	7.46[4]	*	4.66	2.26
KOO	HK	1981-83	22.34	22.61	22.75	19.82	*
LAMT[4]	HK	1983-86	22.75	23.46	23.69	21.33	*
LAMW	HK	1981-84	22.34	22.88	23.69	20.09	*
LEE	Eng/Wal	1979-82	16.28	17.11	17.89	12.60	8.1
PERS[4]	Sweden	1961-80	3.71	5.09	7.56	3.95[4]	*
SHIM[4]	Japan	1982-85	7.46	7.46[4]	7.46	5.65	4.28
SOBU[4]	Japan	1986-88	7.46	7.46[4]	7.46	6.36	4.93
SVEN[4]	Sweden	1983-85	7.72	7.72[4]	7.72	5.78	3.80
TRIC	Greece	1978-80	6.88	6.40	5.99	5.75	5.31[5]
WU	USA	1981-82	17.20	18.15	19.09	10.14	4.96
WUWI[6]	China	1985-87	*	11.6	*	9.2[2]	*

[1] Rates are per 100,000 per year. Annual rates for 2-year periods from Kurihara et al. (1989) were averaged over the years cases were accrued for each study unless otherwise noted. Where part (or all) of the accrual period fell 1 or 2 years outside the years for which rates were available, rates from the nearest 2-year period available were assumed to apply to the missing years. U.S. rates are for white females only.

[2] Data for accrual period from 1978-82 rates in IARC (1987), standardized to 1950 world population from Kurihara et al. (1989). For Correa, weighted average of white and black rates; for Humble, weighted average of Hispanic and non-Hispanic white rates.

Table D-1. (continued)

[3] Accrual period data for Gao and Geng derived from IARC (1987) by standardizing to same 1950 world population used by Kurihara et al. (1989). Gao rates are for 1978-82; Geng, 1981-82. For -10 years, Gao and Geng are 1973-75 rates standardized to the 1960 world population from China Map Press (1979). Gao -20 years value is nonadjusted 1961 rate from Kaplan and Tsuchitani (1978).

[4] Where rates for the period were not available in Kurihara et al. (1989), substitutions were made as follows: Kalandidi from 1984-85 rates; Kabat 1982-83; Katada 1982-83; Lam, T. 1984-85; Pershagen 1952-53; Shimizu 1982-83; Sobue 1982-83; Svensson 1982-83.

[5] World-standardized rate for 1961-65 from Katsouyanni et al. (1990). [In Greek: translation provided by Trichopoulos.]

[6] Accrual period value estimated by multiplying LCMR in Shanghai for period 1978-82 (standardized to the 1950 world population) by the ratio of LCMRs in Liaoning and Heilonjiang to Shanghai, for the period 1973-75 (standardized to the 1960 world population). Data are from China Map Press (1979). Value for -10 years is the 1973-75 rate.

[7] The nested core-control study of Hirayama.

* Data not available.

Table D-2. Parameter values used to partition female lung cancer mortality into component sources[1]

		Ever-smokers		Never-smokers	
Case-Control	Lung Cancer Mortality	Prevalence (%)	Relative Risk	Percent Exposed (%)	Relative Risk
AKIB	6.05	21	2.38	70	1.50
BROW	17.29	29	4.30	15	1.50
BUFF	15.29	59	7.06	84	0.81
CHAN	23.59	26	3.48	47	0.74
CORR	26.00	47	12.40	46	1.90
GAO	18.00	18	2.54	74	1.19
GARF(Coh)	9.45	33	3.50	72	1.15
GENG	27.80	41	2.77	44	2.16
HIRA	5.70	16	3.20	77	1.53
HIRA(Coh)	5.70	16	3.20	77	1.37
HUMB	17.70	41	16.30	56	1.98
INOU	6.53	16	1.66	64	2.55
KABA	13.20	42	5.90	60	0.74
KALA	6.58	17	3.32	60	1.92
KOO	22.61	32	2.77	49	1.54
LAMT	23.46	24	3.77	45	1.64
LAMW	22.88	22	4.12	56	2.51
LEE	17.11	60	4.61	68	1.01
SOBU	7.46	21	2.81	54	1.13
SVEN	7.72	43	5.97	66	1.19
TRIC	6.40	11	2.81	52	2.08
WU	18.15	58	4.38	60	1.31
WUWI	11.60	37	2.24	55	0.78

[1] For studies with data on both ever-smokers and never-smokers. Table entries are drawn from Tables 5-4, B-8 and D-1, which contain explanatory footnotes.

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Table D-3. Female lung cancer mortality rates by attributable source[1]

		Baseline Sources[2]		Spousal Smoking		Ever-smoking	
Study	Location	No.	%	No.	%	No.	%
AKIB	Japan	3.47	57	0.96	16	1.61	27
BROW	USA	8.22	48	0.44	3	8.63	50
BUFF	USA	3.34	22	0.00	0	11.95	78
CHAN	HK	14.34	61	0.00	0	9.25	39
CORR	USA	2.89	11	0.63	2	22.47	86
GAO	China	12.36	69	1.42	8	4.22	23
GARF (Coh)	USA	4.67	49	0.33	4	4.44	47
GENG	China	10.67	38	3.21	12	13.92	50
HIRA (Coh)	Japan	3.28	58	0.78	14	1.63	29
HUMB	USA	1.57	9	0.51	3	15.62	88
INOU	Japan	2.97	45	2.47	38	1.09	17
KABA	USA	4.32	33	0.00	0	8.88	67
KALA	Greece	3.04	46	1.39	21	2.15	33
KOO	HK	11.41	50	2.05	9	9.14	40
LAMT	HK	10.94	47	2.39	10	10.12	43
LAMW	HK	7.35	32	4.85	21	10.68	47
LEE	Eng./Wales	5.37	31	0.01	0	11.73	69
SOBU	Japan	5.05	68	0.28	4	2.13	29
SVEN	Sweden	2.19	28	0.16	2	5.37	70
TRIC	Greece	3.42	53	1.71	27	1.27	20
WU	USA	5.17	28	0.40	2	12.58	69
WUWI	China	7.95	69	0.00	0	3.65	31

[1] Rates are per 100,000 per year. Data not available for GARF, JANE, PERS, SHIM, BUTL(Coh), and HOLE(Coh).
[2] Nonspousal ETS and non-ETS sources.

Table D-4. Lung cancer mortality rates of female ever-smokers (ES) and never-smokers (NS) by exposure status[1]

Study	Location	(1) Unexposed NS[2]	(2) Exposed NS[3]	(3) E.S.	(2) As a Percentage of (3)	(2) - (1) As a Percentage of (3) - (1)
AKIB	Japan	3.47	5.21	11.16	47	23
BROW	USA	8.21	12.32	37.99	32	14
BUFF	USA	3.34	3.34	23.59	14	0
CHAN	HK	14.34	14.34	49.91	29	0
CORR	USA	2.89	5.49	50.70	11	5
GAO	China	12.35	14.70	35.79	41	10
GARF (Coh)	USA	4.67	5.37	18.12	30	5
GENG	China	10.66	23.03	44.62	52	36
HIRA (Coh)	Japan	3.28	4.49	13.49	33	12
HUMB	USA	1.57	3.11	39.66	8	4
INOU	Japan	2.96	7.56	9.80	77	67
KABA	USA	4.32	3.78	25.46	17	0
KALA	Greece	3.04	5.84	15.66	37	22
KOO	HK	11.41	17.57	39.98	44	22
LAMT	HK	10.94	17.94	53.12	34	17
LAMW	HK	7.35	18.45	55.89	33	23
LEE	Eng/Wal	5.36	5.42	24.91	22	0
SOBU	Japan	5.05	5.70	15.18	38	6
SVEN	Sweden	2.18	2.60	14.69	18	3
TRIC	Greece	3.41	7.10	14.99	47	32
WU	USA	5.16	6.77	26.85	25	7
WUWI	China	7.95	7.95	17.81	45	0

[1] Rates are per 100,000 per year. Data not available for GARF, JANE, PERS, SHIM, BUTL(Coh), and HOLE(Coh).
[2] Exposed to baseline sources--nonspousal ETS and non-ETS sources.
[3] Exposed to baseline sources plus spousal ETS.

APPENDIX E. STATISTICAL FORMULAE

E.1. CELL FREQUENCIES

The observed outcome of a case-control study or a cohort study may be depicted in a 2 x 2 table, where a, b, c, and d are cell frequencies.

		ETS Exposed	
		Yes	No
Lung Cancer Present	Yes	a	b
	No	c	d

E.2. CASE-CONTROL STUDIES

The true (but unknown) odds ratio is estimated by the observed odds ratio (OR),

$$OR = ad/bc.$$

A confidence interval on the (true) odds ratio may be calculated from the normal approximation to the distribution of log(OR), the natural logarithm of OR (Woolf, 1955). The variance of log(OR) is estimated by

$$Var(\log(OR)) = 1/a + 1/b + 1/c + 1/d$$

and the standard error by its square root,

$$SE(\log(OR)) = (Var(\log(OR)))^{1/2}.$$

Approximate 90% confidence limits are given by

$$\log(OR) \pm 1.645\ SE(\log(OR)).$$

The value 1.645 is replaced by 1.96 for 95% confidence limits and, in general, by $Z_{\alpha/2}$ for $100(1 - \alpha)$% confidence limits. The confidence bounds obtained in this way are sometimes called *logit limits* (Breslow and Day, 1980; p.134). Significance level (P-value) of a test for effect, i.e., H_o: (true) odds ratio = 1 against the alternative H_a: (true) odds ratio > 1, is the area under the standard normal curve to the right of the value of the *test statistic*, given by log(OR)/SE(log(RR)).

If the (true) odds ratios are assumed to be equal in k studies, then a pooled estimate is calculated from

$$\log(OR(P)) = \sum w_i \log(OR)_i / \sum w_i$$

where the summations are on i, from 1 to k; OR(P) is the pooled estimate; $\log(OR)_i$ is the logarithm of OR from the i^{th} study; and $w_i = (Var(\log(OR)_i))^{-1}$ is the *weight* of the i^{th} study (Breslow and Day, 1980).

E.3. COHORT STUDIES

The true (but unknown) relative risk is estimated by the observed relative risk (RR),

$$RR = (a/a+c)/(b/b+d).$$

A confidence interval on the (true) relative risk may be calculated from the normal approximation to the distribution of log(RR), using the analogue of Woolf's method referred to above (Katz et al., 1978). The variance of log(RR) is estimated by,

$$Var(\log(RR)) = c/(a^2 + ac) + d/(b^2 + bd)$$

and the standard error by its square root,

$$SE(\log(RR)) = (Var(\log(RR)))^{½}.$$

The remaining calculations follow the description for case-control studies in Section E.2 with "odds ratio" and "OR" replaced by "relative risk" and "RR," respectively. The pooled estimate of relative risk from both case-control and cohort studies is calculated by the same methodology for pooling estimates from case-control studies or from cohort studies separately, i.e., the logarithm of each individual estimate is weighted inversely proportional to its estimated variance (Kleinbaum et al., 1982).

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